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(54) Title: COMPOSITION COMPRISING SEROTONIN RECEPTOR ANTAGONISTS, 5 HT-2 AND 5 HT-3

(57) Abstract: A composition comprising a combination of compounds comprising: a) at least one compound with antagonist activity to the 5-HT<sub>3</sub> receptor; and b) at least one compound with antagonist activity to the 5-HT<sub>2</sub> receptor is described.



**WO 02/36114 A1**

COMPOSITION COMPRISING SEROTONIN RECEPTOR ANTAGONISTS,  
5 HT-2 and 5 HT-3.

Field of the Invention

The present invention relates to a composition comprising a combination of a) at least one compound with antagonist activity to the 5-HT<sub>3</sub> receptor and b) at least one compound with antagonist activity to the 5-HT<sub>2</sub> receptor, to a composition as defined above for use as a medicament, to the use of said composition in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving airway constriction in humans or animals, and to a method of treatment of such disorders, wherein said compound is administered.

Background of the Invention

There are seven main types of 5-HT (serotonin; 3-( $\beta$ -aminoethyl)-5-hydroxyindole) receptors, (5-HT<sub>1-7</sub>). These receptors occur throughout the body, e.g. in the airways, and have mainly been reported to be of significance in conjunction with treatment of CNS, muscle and gastric disorders. In such treatments, compounds with agonist activity to a 5-HT<sub>1</sub> type receptor are often used. For a recent review of 5-HT receptors, see Gerhardt, C.C. & van Heerikhuizen, H., Eur. J. Pharm., 334, 1-23 (1997), which is incorporated herein by reference. For a review of typical agonists and antagonists of various 5-HT receptors, see R.A. Glennon, Neuroscience and Biobehavioral Reviews, 14, 35-47 (1990), the whole content of which is incorporated herein by reference. Further information regarding 5-HT receptors and their agonists and antagonists can be found in the RBI Handbook of Receptor Classification and Signal Transduction, 3<sup>rd</sup> Edition, 1998, RBI, One Strathmore Road, Natick, MA 01760-2447, USA, Editor: Keith J. Watling, which is also incorporated herein by reference.

SU 1 701 320 A1 discloses the use of the unspecific 5-HT receptor agonist for treatment of acute asthma attacks. However, the present application do not refer to the use of 5-HT receptor agonists (such as 5-HT), but rather 5-HT receptor antagonists.

#### Disclosure of the Invention

The present invention is based on the novel finding that certain 5-HT receptors are of the utmost importance in determining the level of airway constriction. In summary, it is disclosed herein that the administration of a composition comprising a combination of compounds comprising a) at least one compound with antagonist activity to the 5-HT<sub>3</sub> receptor and b) at least one compound with antagonist activity to the 5-HT<sub>2</sub> receptor, causes a distinct airway relaxation, and is therefore suitable as an agent for treatment of disorders involving airway constriction. A method for treatment of disorders involving airway constriction is also disclosed.

As used herein, the expression "airway constriction" refers to an abnormal increase of force development of the smooth muscle in human or animal airways, resulting in a reduced diameter in some or all of the airways, such as occurring in asthma, chronic obstructive pulmonary disease, emphysema and chronic bronchitis. Said expression also refers, in a wider sense, to a reduction of the airway diameter caused by swelling, oedema, plasma extravasation or mucous secretion caused by e.g. asthma or any other disorder related thereto.

The expression "has the capacity of reducing the abnormal airway constriction by at least ....%" used in the present patent application means that the combination of compounds in question reduces, to a certain degree, airway constriction caused either by (1) the underlying disease (asthma etc) or (2) the administration of 5-HT or other substances capable of activating constricting 5-HT receptors. The level of constriction in the airways can e.g. be determined by spirometric measurements of the

Forced Expiratory Volume in 1 second (FEV1), compared to the normal value for healthy people. Alternatively, the expiratory capacity for a patient can be compared to his own FEV1 during periods of relatively little obstructive problems.

The present invention relates, in one of its aspects, to a composition comprising a combination of compounds comprising a) at least one compound with antagonist activity to the 5-HT<sub>3</sub> receptor and b) at least one compound with antagonist activity to the 5-HT<sub>2</sub> receptor. In another aspect, the present invention relates to a composition as defined above for use as a medicament.

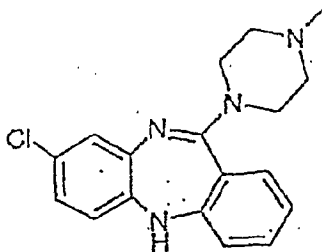
In still another aspect it relates to the use of said composition in the manufacture of a medicament for therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving airway constriction, such as asthma, chronic obstructive pulmonary disease, emphysema and chronic bronchitis.

The combination of a) at least one 5-HT<sub>3</sub> receptor antagonist and b) at least one 5-HT<sub>2</sub> receptor antagonist increases airway relaxation compared to the use of either compound alone, wherein said combination has the capacity of reducing the abnormal airway constriction by at least 30%, preferably at least 60%, and most preferably at least 90%.

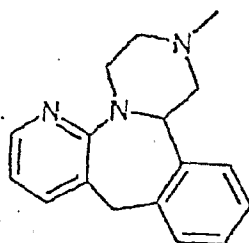
According to the present invention, several known 5-HT<sub>3</sub> antagonist and 5-HT<sub>2</sub> antagonist compounds are, unexpectedly, able to induce airway relaxation.

The 5-HT<sub>3</sub> receptor is a ligand modulated ion channel. Several potent and specific 5-HT<sub>3</sub> antagonists exist today, of which ondansetron, tropisetron, granisetron, and dolasetron are commercial pharmaceuticals, but not against disorders involving airway constriction. The following 5-HT<sub>3</sub> receptor antagonists are contemplated according to the present invention:

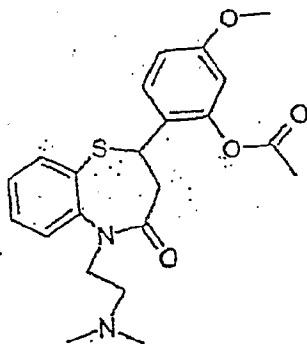
a) The 5-HT<sub>3</sub> antagonists may be divided into certain classes on the basis of chemical structure. Some are un-specific, e.g.



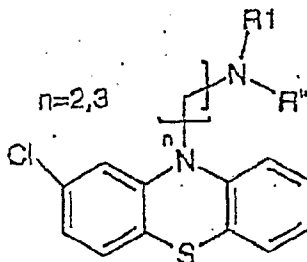
benzazepines, e.g. mirtazapine



benztiazepines, e.g. diltiazem

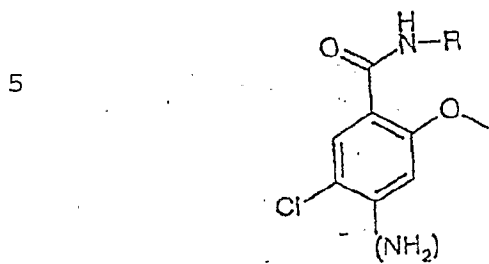


and fentiazines



e.g. perphenazine, chlorpromazine, stemetil.

Some are 5-HT<sub>4</sub> agonists, e.g. benzamides

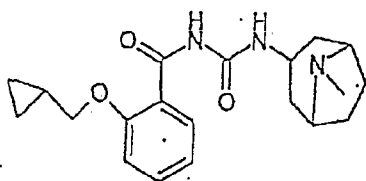


(cisapride, zacopride,  
mosapride, metoclopra-  
mide, pancropride,  
BRL 24924, BMY 33462)

10

and

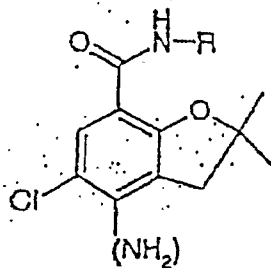
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WAY 100289

2,3-dihydro-benzofuran-7-carboxamides

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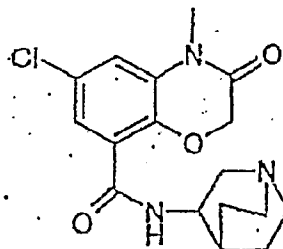


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(e.g. zatosetron=LY 277359, ADR 851);

1,4-benzoxazin-8-carboxamides

30

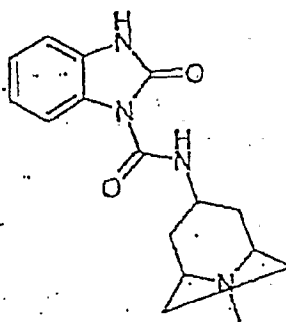


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e.g. azasetron (=Y25130)

benzimidazolones

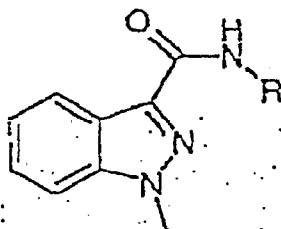
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10 e.g. itasetron (=DAU 6215);

indazol-3-carboxamides

15

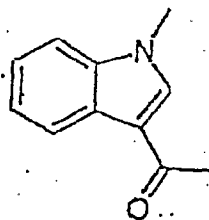


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e.g. N 3389, LY 278584, DAT 582

The latter group reminds most of the specific 5-HT<sub>3</sub> antagonists, which contains the group

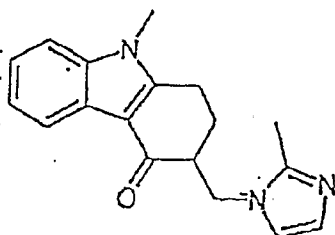
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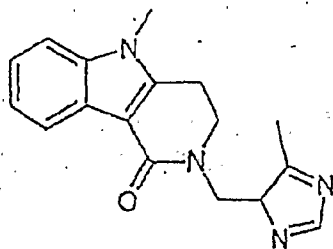
in different forms, such as

35

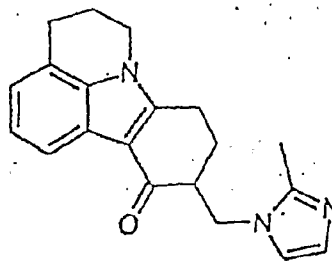


ondansetron

5



alosetron

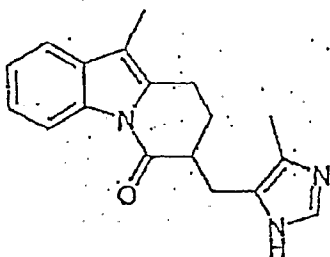


cilansetron

10

In one group of substances the structure has been inverted and the carbonyl group has been placed on the indoline nitrogen

15

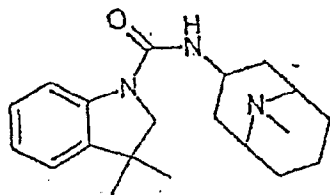


FK 1052

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This substance is unique by being an antagonist against both 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors.

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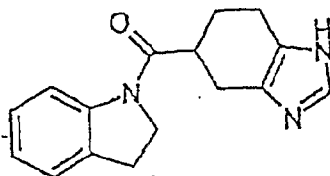
BRL 46470 A

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BRL 46470A binds to two different positions of the receptor.

A further development is the so-called bisindoles

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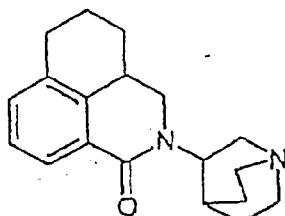


YM 114

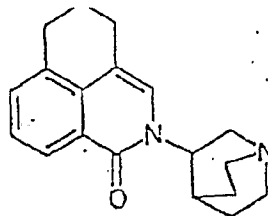


Another group is the isoquinoline-1-ones

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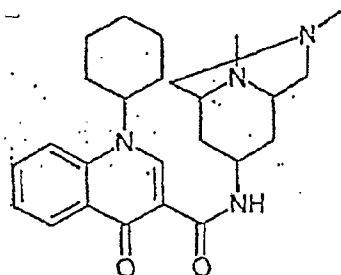
palonosetron (=RS 25259-197)



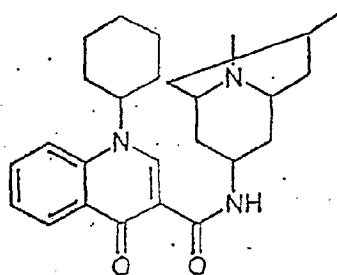
RS 42358-197

10 and the quinoline-3-carboxamides

15



WAY-SEC 579

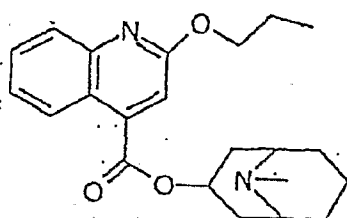


Mirisetron (=WAY 100579)

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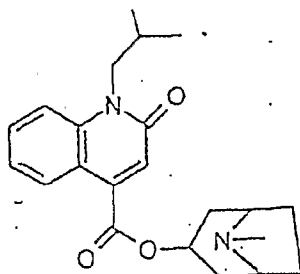
Also the quinoline-4-carboxylates are active antagonists

25



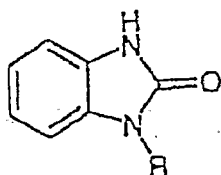
30 e.g. KF 17643

35

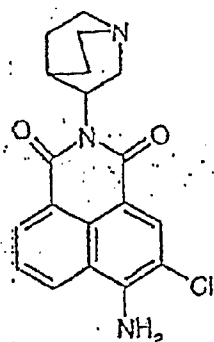


e.g. KF 18259

Other compounds are benzimidazolones

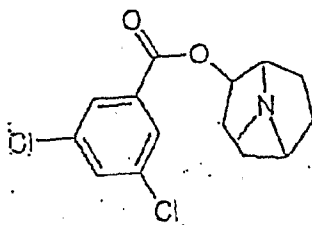


e.g. droperidol (neurolidol, etc.), itasetron (DAU6215),  
and the naphtimides



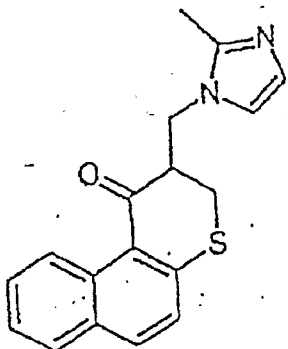
e.g. RS 56532

A unique single structure is MDL 72222, which also  
is a specific 5-HT<sub>3</sub> antagonist



Other specific structures are

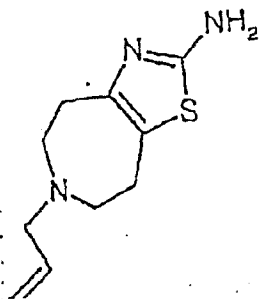
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GK 128

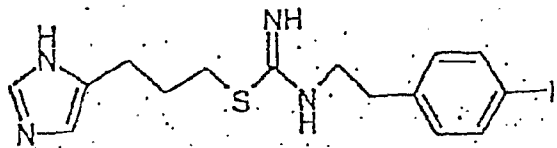
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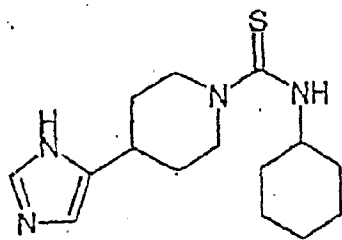
Talipexole

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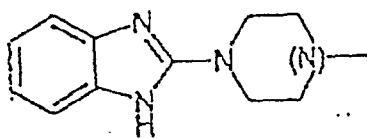
iodophenpropit

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thioperamide, and

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2-piperidin- and 2-piperazin-  
benzimidazoles.

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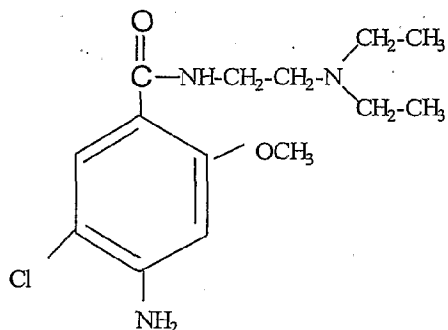
According to the present invention, the following compounds can also be used as antagonists to the 5-HT<sub>3</sub>

receptor: (R)-zacopride, 2-methyl-5HT, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, 3-(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, 5,7-DHT, 5-[(dimethylamino)methyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, AS-5370, Batanopride, BIMU 1, BRL 24682, BRL 43694, BRL 46470 (=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyameazine, Cyproheptadine, Dolasetron, Dolasetron mesilat (=MDL 73147 EF), Fluphenazone, Galdanasetron, GR 38032 F, GR 67330, Granisetron (=Kytril=BRL 43694), GR-H, GYKL-48903, ICS 205-930, Imipramine, Indalpine, KAE-393/YM-114, KB-6922, KB-6933, KB-R 6933, KF-20170, Lerisetron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCPP, MDL 72699, Mepyramine, Metergoline, Methysergide, Mianserin, MK 212, N-3256, NAN-190, N-methylquipazin, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, ONO-3051, Pancopride, Phenylbiguanide, Pitozifen, Prochlorperazine, QICS 205-930, R(+)zacopride, Renzapride, RG 12915, Ritanserin, RP 62203, RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-apomorfin, SC-52491, SC-53116, SDZ 206-792, SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TMPP, TMB 8, trifluoperazine, tropanyl-3,5-dimethylbenzoate, 3-tropanyl-indole-3-carboxylate methiodide, tropisetron, VA 21 B 7, Y 2513, zelmac, SEC 579, BRL 46470 A, Pizotifen, Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, Litoxetine, Quipazine, QX 222, Ramosetron (=YM 060), RS 56812, SDZ 216-525, Trimebutine, GR 65630, Tropisetron, Bemisetron, L-683,877, LY-278, 584 maleate and pharmaceutically acceptable salts thereof with the same or essentially the same relaxation enhancing effect.

In the following, an alternative presentation of useful compounds according to the present invention and references thereto is listed.

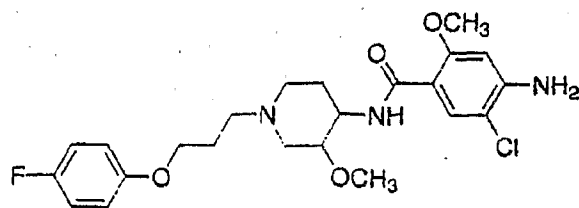
N-substituted benzamides

- Metoclopramide



- 5      • QX 222. The compound is an analogue to lidocain<sup>®</sup>, which is a N-substituted benzamide derivative.
- 10      • Cisapride (Cizapride) cis-4-Amino-N-[1-[3-(p-fluorophenoxy)propyl]-3-methoxy-4-piperidyl]-5-chloro-o-anisamide. The compound is also a known 5-HT<sub>4</sub> agonist.

*cis*-4-Amino-N-[1-[3-(*p*-fluorofenoxy)propyl]-3-metoxi-4-piperidyl]-5-kloro-*o*-anisamid



- Pancopride ((+/-)N-(1-azabicyclo-[2,2,2]-oct-3-yl)-2-cyclopropylmethoxy-4-amino-5-chlorobenzamide)  
Pancopride, a potent and long-acting 5-HT<sub>3</sub> receptor antagonist, is orally effective against anticancer drug-evoked emesis., Fernández AG, Puig J, Beleta J, Doménech T, Bou J, Berga P, Gristwood RW, Roberts DJ; *Eur J Pharmacol* 1992 Nov 10, 222:2-3:257-64

Pancopride ((+/-)N-(1-azabicyclo-[2,2,2]-oct-3-yl)-2-cyclopropylmethoxy-4-amino-5-chlorobenzamide) is a new potent and selective 5-HT<sub>3</sub> receptor antagonist, orally and parenterally effective against cytotoxic drug-induced emesis. In vitro, pancopride displayed high affinity ( $K_i = 0.40$  nM) for [<sup>3</sup>H]GR65630-labelled 5-HT<sub>3</sub> recognition sites in membranes from the cortex of rat brains. In vivo, pancopride antagonized 5-HT-induced bradycardia in anaesthetized rats when administered i.v. 5 min ( $ID_{50} = 0.56$  microgram/kg) or p.o. 60 min ( $ID_{50} = 8.7$  micrograms/kg) before 5-HT challenge. A single oral dose (10 micrograms/kg) of pancopride produced a significant inhibition of the bradycardic reflex over an 8-h period. Pancopride dose dependently inhibited the number of vomiting episodes and delayed the onset of vomiting induced by cisplatin in dogs ( $ID_{50} = 3.6$  micrograms/kg i.v. and 7.1 micrograms/kg p.o.). Pancopride was also effective in blocking mechlorethamine- and dacarbazine-induced emesis. Unlike metoclopramide, pancopride was shown to lack any measurable antidopaminergic activity both in vitro and in vivo. These results support clinical data, indicating that pancopride will be a useful drug for treating cytostatic-induced emesis in humans.

- (R)-zacopride (R+ zacopride, zacopride) IUPAC name: 4-amino-N-(1-azabicyclo[2.2.2] oct-3yl)-5-chloro-2-methoxy-benzamide.

5 The differential activities of R (+)- and S (-)-zacopride as 5-HT<sub>3</sub> receptor antagonists.

Barnes JM, Barnes NM, Costall B, Domeney AM, Johnson DN, Kelly ME, Munson HR, Naylor RJ, Young R;

Pharmacol Biochem Behav 1990 Dec, 37:4:717-27

10 R(+)- and S(-)-zacopride were assessed as potential 5-HT<sub>3</sub> receptor antagonists in behavioural and biochemical tests. The S(-)isomer was more potent than the R(+)isomer to antagonise the hyperactivity induced by the injection of amphetamine or the  
15 infusion of dopamine into the nucleus accumbens in the rat. In contrast, the R(+)isomer was more potent to reduce the aversive behaviour of mice to a brightly illuminated environment and in a marmoset human threat test, to facilitate social interaction  
20 in rats, to increase performance in a mouse habituation test and prevent a scopolamine-induced impairment, and to antagonise the inhibitory effect of 2-methyl-5-hydroxytryptamine to reduce [3H]acetylcholine release in slices of the rat  
25 entorhinal cortex. In binding assays, [3H]S(-)-zacopride and [3H]R(+)-zacopride labelled homogenous populations of high-affinity binding sites in the rat entorhinal cortex, R(+)-zacopride compete for a further 10 to 20% of the binding of [3H]R(+)/S(-)-  
30 zacopride or [3H]R(+)-zacopride in excess of that competed for by (S) (-)-zacopride. It is concluded that both isomers of zacopride have potent but different pharmacological activities, with the possibility of different recognition sites to  
35 mediate their effects.

- BRL 24682  
The compound is also a known 5-HT<sub>4</sub> agonist.
- BRL 24924  
5 [(+/-)-(endo))-4-amino-5-chloro-2-methoxy-N-(1-azabicyclo-[3.3.1]-non-4-yl) benzamide hydrochloride. The compound is also a known 5-HT<sub>4</sub> agonist.
- 10 • Mosapride ((4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl] benzamide citrate.
- Renzapride= BRL 24924; see above
- 15 • SC-52491 (Azanoradamantane)
- SC-53116 ((1-S,8-S)-4-amino-5-chloro-N-[(hexahydro-1H-pyrrolizin-1-yl) methyl]-2-methoxy-benzamide hydrochloride)
- 20 • Batanopride (4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-(1-methyl-2-oxopropoxy) benzamide). Batanopride is also known by the name
- 25 BMY-25801.
- WAY 100289

*Indoles, Indole-1-carboxamides and Imidazole derivatives*

30

- 2-methyl-5-HT
- 5,7-DHT= 5,7-dihydroxy-tryptamine
- 35 • Bisindoles
- Bufotenine =(5-hydroxy-N,N-dimethyltryptamine)



- BRL 46470A (endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3,3-dimethyl-indole-1-carboxamide, hydrochloride)
  - BRL 46470 (endo-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3,3-dimethyl-indole-1-carboxamide HCl)
  - BRL 47204
  - FK 1052 ((+)-8,9-dihydro-10-methyl-7-[(5-methyl-1H-imidazol-4-yl)methyl]pyrido[1,2-a]indol-6(7H)-one hydrochloride)
- Pharmacological characterization of FK1052, a dihydropyridoindole derivative, as a new serotonin 3- and 4 dual receptor antagonist., Nagakura Y, Kadowaki M, Tokoro K, Tomoi M, Mori J, Kohsaka M; J Pharmacol Exp Ther 1993 May, 265:2:752-8
- (+)-8,9-Dihydro-10-methyl-7-[(5-methyl-4-imidazolyl)methyl]pyrido-[1,2-a]indol-6(7H)-one hydrochloride (FK1052) is a newly designed and synthesized 5-hydroxytryptamine (5-HT)<sub>3</sub> receptor antagonist with 5-HT<sub>4</sub> receptor antagonistic activity. This compound, as well as ondansetron and granisetron, dose-dependently inhibited the von Bezold-Jarish reflex, a 5-HT<sub>3</sub> receptor-mediated response, after intravenous (i.v.) and intraduodenal (i.d.) dosing to rats. The ID<sub>50</sub> values showed FK1052 (0.28 microgram/kg, i.v., 5.23 micrograms/kg, i.d.) to be more potent than ondansetron (5.23 micrograms/kg, i.v., 170 micrograms/kg, i.d.) and granisetron (0.70 micrograms/kg, i.v., 66 micrograms/kg, i.d.). Furthermore, bioavailabilities of the test drugs by ID<sub>50</sub> ratio (i.d./i.v.) showed

that FK1052(17) was better absorbed than ondansetron(33) and granisetron(94) and possessed a similar duration of action to that of ondansetron and granisetron. We also examined the effects on 2-methyl-5-HT-, 5-HT- and 5-methoxytryptamine-induced contractions of guinea pig isolated ileum. FK1052, ondansetron and granisetron concentration-dependently inhibited 2-methyl-5-HT, a 5-HT<sub>3</sub> agonist-induced contraction. The pA<sub>2</sub> values for the 5-HT<sub>3</sub> receptor indicated that FK1052 (8.36) was 40 times and three times more potent than ondansetron (6.79) and granisetron (7.86), respectively. FK1052, unlike ondansetron and granisetron, inhibited the 5-HT<sub>4</sub>-mediated component of concentration-response curve to 5-HT. Furthermore, FK1052 suppressed 5-methoxytryptamine, a 5-HT<sub>4</sub> agonist-induced contraction in a concentration-dependent but insurmountable manner.

- RU 24969 (5-methoxy-3(1,2,3,6-tetrahydropyridin-4-yl)-1 H-indole)

- SDZ 206-792

Characterisation of 5-HT<sub>3</sub> recognition sites in membranes of NG 108-15 neuroblastoma-glioma cells with [3H]ICS 205-930. Neijt HC, Karpf A, Schoeffter P, Engel G, Hoyer D Naunyn Schmiedeberg's Arch Pharmacol 1988 May, 337:5:493-9

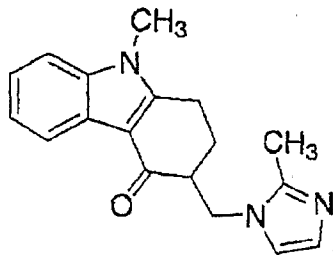
1. The binding characteristics of [3H]ICS 205-930, a potent and selective 5-hydroxytryptamine 5-HT<sub>3</sub> receptor antagonist, were investigated in membranes prepared from murine neuroblastoma-glioma NG 108-15 cells. 2. [3H]ICS 205-930 bound rapidly, reversibly and stereoselectively to a homogeneous population of high affinity recognition sites: B<sub>max</sub> = 58 +/- 3

fmol/mg protein,  $pK_D = 9.01 \pm 0.08$  ( $n = 11$ ). Non linear regression and Scatchard analysis of saturation data suggested the existence of a single class of [3H]ICS 205-930 recognition sites on NG 108-15 cells. The binding was rapid, stable and reversible. The affinity of [3H]ICS 205-930 determined in kinetic studies was in agreement with that obtained under equilibrium conditions. 3. Competition studies performed with a variety of agonists and antagonists also suggested the presence of a homogeneous population of [3H]ICS 205-930 recognition sites. All competition curves were steep and monophasic and were best fit by a 1 receptor site model. [3H]ICS 205-930 binding sites displayed the pharmacological profile of a 5-HT<sub>3</sub> receptor. Potent 5-HT<sub>3</sub> receptor antagonists showed nanomolar affinities for [3H]ICS 205-930 binding sites with the following rank order of potency: SDZ 206-830 greater than ICS 205-930 greater than SDZ 206-792 greater than BRL 43694 greater than quipazine greater than BRL 24924 greater than SDZ 210-204 greater than MDL 72222 greater than SDZ 210-205. Metoclopramide, MCP and mianserin showed submicromolar affinity.

- Ondansetron=GR 38032F=SN-307=Zofran®

### Ondansetronum INN (Ondansetron)

2,3-Dihydro-9-methyl-3-[(2-methylimidazol-1-yl)methyl]karbazol-4(1H)-on



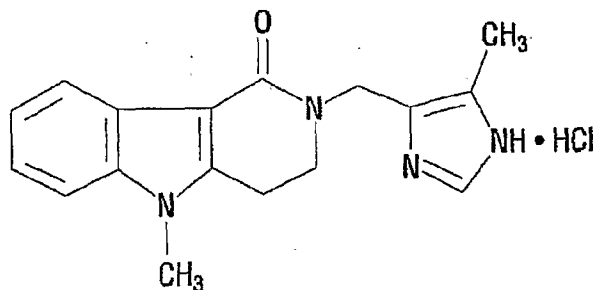
The compound is both an indole derivative and an imidazole. Other imidazole derivatives are listed below.

- 5     • GR 38032 F  
Comparison of the 5-HT<sub>3</sub> receptor antagonist properties of ICS 205-930, GR38032F and zacopride., Cohen ML, Bloomquist W, Gidda JS, Lacefield W; J Pharmacol Exp Ther 1989 Jan, 10     248:1:197-201

The well-documented 5-HT<sub>3</sub> receptor antagonists, ICS 205-930 and GR38032F, have been compared with regard to their inhibitory activity at 5-HT<sub>3</sub> receptors to another gastrokinetic agent, zacopride. Zacopride and ICS 205-930 showed similar affinity (-log k<sub>B</sub> approximately 8.0), whereas GR38032F showed lower affinity (-log k<sub>a</sub> approximately 7.0) at 5-HT<sub>3</sub> receptors in the guinea pig ileum. After i.v. administration to anesthetized rats, zacopride was approximately 10-fold more potent than either ICS 205-930 or GR38032F, which were equipotent as inhibitors of serotonin-induced bradycardia (5-HT<sub>3</sub>-mediated activation of the von Bezold Jarisch reflex). After oral administration to anesthetized rats, zacopride remained approximately 10-fold more potent than ICS 205-903, which was approximately 2-fold more potent than GR38032F as an inhibitor of serotonin-induced bradycardia. Furthermore, the inhibitory effectiveness of GR38032F persisted for less than 3 hr after oral administration and for less than 15 min after intravenous administration. ICS 205-930 produced maximal inhibition of serotonin-induced bradycardia for over 3 hr with heart rate returning to control values 6 hr after oral administration. Zacopride possessed the longest duration of inhibitory effectiveness in urethane-

anesthetized rats with maximal inhibition still  
apparent 6 hr after oral administration. All three  
agents inhibited cisplatin-induced emesis after i.v.  
administration in dogs with zacopride being 10-fold  
more potent than ICS 205-930 or GR38032F, which were  
equipotent. These comparative data with three 5-HT<sub>3</sub>  
receptor antagonists indicate that in animals,  
zacopride was more potent and longer acting than  
either ICS 205-930 or GR38032F. Furthermore, after  
oral administration to rats, GR38032F was slightly  
less potent than ICS 205-930 and possessed the  
shortest duration of action.

- Alosetron=Lotronex (Glaxo)



The compound is both an indole derivative and an  
imidazole. Other imidazole derivatives are listed  
below.

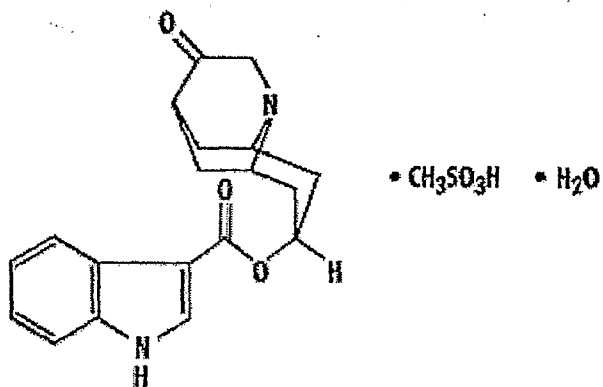
The pharmacological properties of the novel selective  
5-HT<sub>3</sub> receptor antagonist, alosetron, and its effects  
on normal and perturbed small intestinal transit in  
the fasted rat., Clayton NM, Sargent R, Butler A, Gale  
J, Maxwell MP, Hunt AA, Barrett VJ, Cambridge D,  
Bountra C, Humphrey PP; Neurogastroenterol Motil 1999  
Jun, 11:3:207-17

The purpose of this study was to investigate the pharmacological properties of the novel, selective 5-HT<sub>3</sub> receptor antagonist, alosetron, and its effects on transit time in both the normal and perturbed small intestine of the rat. Alosetron concentration-dependently inhibited radioligand binding in membranes containing rat and human 5-HT<sub>3</sub> receptors with estimated pK<sub>i</sub> values of 9.8 (n = 3) and 9.4 (n = 6), respectively. In selectivity studies alosetron had little or no significant affinity for any of the many other receptors and ion channels studied. Alosetron potently antagonized the depolarization produced by 5-HT in the rat vagus nerve (estimated pK<sub>B</sub> value of 9.8, n = 25). In anaesthetized rats, i. v. administration of alosetron inhibited 2-methyl-5-HT induced bradycardia (Bezold Jarisch index) at 1 and 3 microg kg<sup>-1</sup>, with an agonist dose ratio of approximately 3.0 at 1.0 microg kg<sup>-1</sup>, (= 3-5). Alosetron administered via the duodenum also inhibited this reflex, with duration of action that was significantly longer than that seen with ondansetron (120-60 min, respectively, n = 6). Alosetron had no significant effect on normal small intestinal propulsion in the rat, but fully reversed the increase in intestinal propulsion (96%, n = 3) produced by egg albumin challenge. Alosetron is a highly selective 5-HT<sub>3</sub> antagonist which normalizes perturbed small intestinal propulsion. Previous clinical data in IBS patients together with the transit data provide a good rationale for further studies with alosetron in IBS patients.

- Bemasetron
- Galdansetron
- Dolasetron mesilat =MDL73147 EF= Anzemet.

22

IUPAC name: (2,6,8,9a $\beta$ )-octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-1H-indole-3-carboxylate monomethanesulfonate, monohydrate.

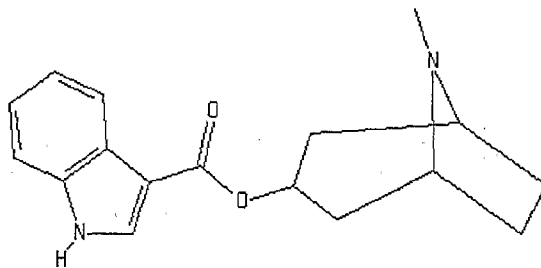


5

- Dolasetron=MDL74156

- Tropisetron =Navoban®

10 IUPAC name: 1aH,5aH - Tropane - 3a - yl-3 - indole-carboxylate



- Zatosetron =LY 277359. The compound is also called LY 19617.

15

The effect of acute and chronic LY 277359, a selective 5-HT<sub>3</sub> receptor antagonist, on the number of spontaneously active midbrain dopamine neurons., Minabe Y, Ashby CR Jr, Wang RY; Eur J Pharmacol 1991 Dec 17, 209:3:151-6

In this study, we have examined the effect of acute and chronic administration of LY 277359, a putative 5-HT<sub>3</sub> receptor antagonist, on the number of spontaneously active dopamine cells in the substantia nigra pars compacta (SNC or A9) and ventral tegmental area (VTA or A10). This was accomplished using the standard extracellular single unit recording techniques. The acute administration of LY 277359 (0.1 or 1.0 mg/kg i.p.) produced a significant increase in the number of spontaneously active A10, but not A9, dopamine cells compared to saline controls. The acute administration of 10 mg/kg of LY 277359 did not significantly alter the number of spontaneously active dopamine cells in either area. In contrast to its acute effects, the administration of 0.1 mg/kg per day of LY 277359 for 21 days decreased the number of spontaneously active A9 and A10 dopamine cells. However, the i.v. administration of (+/-)-apomorphine (50 micrograms/kg) did not reverse LY 277359's action, suggesting that the chronic LY 277359-induced reduction of dopamine cells was not the result of depolarization block. To test whether chronic administration of LY 277359 at a high dose would induce depolarization block of dopamine cells, rats were treated with 1.0 or 10 mg/kg LY 277359. Interestingly, the chronic administration of 1.0 mg/kg LY 277359 increased the number of A10, but not A9 dopamine cells. In contrast, chronic treatment with 10 mg/kg selectively decreased the number of spontaneously active A10 dopamine cells.



- GR65630 (3-(5-methyl-1H-imidazol-4-yl)-1-(1-methyl-1H-indol-3-yl)-1-propanone)

5 • GR67330

[3H] GR67330, a very high affinity ligand for 5-HT<sub>3</sub> receptors.

Kilpatrick GJ, Butler A, Hagan RM, Jones BJ, Tyers MB Naunyn Schmiedebergs Arch Pharmacol 1990 Jul, 342:1:22-30

GR67330 potently inhibited 5-hydroxytryptamine (5-HT)-induced depolarizations of the rat isolated vagus nerve. At the higher concentrations used (0.3 nmol/l-1 nmol/l) this was accompanied by a marked reduction in the maximum response to 5-HT. The calculated pK<sub>B</sub> value was 10.2. The binding of the tritiated derivative of GR67330 to homogenates of rat entorhinal cortex was examined. Kinetic analysis revealed that specific [3H] GR67330 (0.1 nmol/l) binding was rapid and reversible. Association and dissociation rate constants were  $1.48 \pm 0.36 \times 10^8 \text{ mol/l}^{-1} \text{ s}^{-1}$  and  $7.85 \pm 0.41 \times 10^{-3} \text{ s}^{-1}$  respectively. Equilibrium saturation analysis revealed specific binding was to a single site (B<sub>max</sub>  $22.6 \pm 0.21 \text{ fmol/mg protein}$ ) of high affinity (K<sub>d</sub>  $0.038 \pm 0.003 \text{ nmol/l}$ ). At low ligand concentrations, specific binding was up to 90% of total binding. If unlabelled GR67330 was used to define non-specific binding two sites were evident (K<sub>d1</sub>  $0.066 \pm 0.007 \text{ nmol/l}$ , K<sub>d2</sub>  $20.1 \pm 9.7 \text{ nmol/l}$ ; B<sub>max1</sub>  $31.5 \pm 3.2 \text{ fmol/mg protein}$ , B<sub>max2</sub>  $1110 \pm 420 \text{ fmol/mg protein}$ ). [3H] GR67330 binding was inhibited potently by 5-HT<sub>3</sub> antagonists and agonists. Ligands for other 5-HT receptors and other neurotransmitter receptors were either only weakly active or inactive at inhibiting binding. Hill

numbers for antagonist inhibition of binding were close to unity, except for quipazine which was significantly greater than one. In common with other 5-HT<sub>3</sub> binding studies, all 5-HT<sub>3</sub>-agonist tested had Hill numbers greater than one (1.51-1.71). GR38032 and GR65630 inhibited a greater proportion of binding than other 5-HT<sub>3</sub> antagonists, this additional binding was interpreted as inhibition from a second saturable site unrelated to the 5-HT<sub>3</sub> receptor.

- ICS 205-930 ((3 Alpha-Tropanyl)-1H-Indole-3-carboxylic acid ester)

Comparison of the 5-HT<sub>3</sub> receptor antagonist properties of ICS 205-930, GR38032F and zacopride., Cohen ML, Bloomquist W, Gidda JS, Lacefield W J Pharmacol Exp Ther 1989 Jan, 248:1:197-201

The well-documented 5-HT<sub>3</sub> receptor antagonists, ICS 205-930 and GR38032F, have been compared with regard to their inhibitory activity at 5-HT<sub>3</sub> receptors to another gastrokinetic agent, zacopride. Zacopride and ICS 205-930 showed similar affinity (-log K<sub>B</sub> approximately 8.0), whereas GR38032F showed lower affinity (-log K<sub>A</sub> approximately 7.0) at 5-HT<sub>3</sub> receptors in the guinea pig ileum. After i.v. administration to anesthetized rats, zacopride was approximately 10-fold more potent than either ICS 205-930 or GR38032F, which were equipotent as inhibitors of serotonin-induced bradycardia (5-HT<sub>3</sub>-mediated activation of the von Bezold Jarisch reflex). After oral administration to anesthetized rats, zacopride remained approximately 10-fold more potent than ICS 205-903, which was approximately 2-fold more potent than GR38032F as an inhibitor of serotonin-induced bradycardia. Furthermore, the inhibitory effectiveness of GR38032F persisted for

less than 3 hr after oral administration and for less than 15 min after intravenous administration. ICS 205-930 produced maximal inhibition of serotonin-induced bradycardia for over 3 hr with heart rate returning to control values 6 hr after oral administration. Zacopride possessed the longest duration of inhibitory effectiveness in urethane-anesthetized rats with maximal inhibition still apparent 6 hr after oral administration. All three agents inhibited cisplatin-induced emesis after i.v. administration in dogs with zacopride being 10-fold more potent than ICS 205-930 or GR38032F, which were equipotent. These comparative data with three 5-HT<sub>3</sub> receptor antagonists indicate that in animals, zacopride was more potent and longer acting than either ICS 205-930 or GR38032F. Furthermore, after oral administration to rats, GR38032F was slightly less potent than ICS 205-930 and possessed the shortest duration of action.

- QICS 205-930
- 3-Tropanyl-indole-3-carboxylate methiodide. It is also called ICS 205-930.
- Indalpine (3-[2-(4-piperidinyl)ethyl]-1H-indole)
- VA21B7 (3-[2-(4'-piperonylpiperazinyl) indolyl] carboxaldehyde)

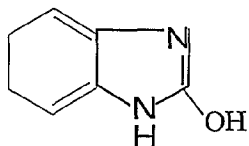
The pharmacology of VA21B7: an atypical 5-HT<sub>3</sub> receptor antagonist with anxiolytic-like properties in animal models. Artaiž I, Romero G, Zazpe A, Monge A, Calderó JM, Roca J, Lasheras B, Del Río J *Psychopharmacology* (Berl) 1995 Jan, 117:2:137-48

VA21B7 (3-[2-(4'-piperonylpiperaziny] indolyl] carboxaldehyde) was synthesized as a potential 5-HT<sub>3</sub> receptor antagonist. Even though VA21B7 showed a higher affinity towards 5-HT<sub>3</sub> receptors as compared to other receptors studied, it was not a potent 5-HT<sub>3</sub> receptor antagonist either in the periphery or in the brain. In a simple animal model of anxiety such as the two-compartment box in mice, a remarkable anxiolytic-like effect was found at doses of 2-500 micrograms/kg IP and also at low oral doses, in the microgram range. These drug doses did not produce any significant effect on spontaneous motor activity of mice. The anxiolytic profile of VA21B7 was further explored using other models of anxiety in rats such as the elevated plus-maze and punished-drinking. VA21B7 was compared with standard 5-HT<sub>3</sub> receptor antagonists such as ondansetron, tropisetron and granisetron, with the 5-HT<sub>1A</sub> agent buspirone and with diazepam. In the plus-maze, VA21B7 showed an anxiolytic-like profile after doses of 0.25-0.5 mg/kg IP or 2-4 mg/kg PO which did not modify the number of total entries into the open and closed arms of the maze. Diazepam, granisetron and tropisetron were also effective in this test but not ondansetron and buspirone. VA21B7 was also able to release suppressed behaviour in the punished-drinking test. The dose-response curve was bell-shaped with a peak at 2-4 mg/kg. At variance with other studies, 5-HT<sub>3</sub> receptor antagonists also increased the number of shocks taken in this test and the dose-response curve was also bell-shaped. VA21B7 was not anticonvulsant like diazepam, its anxiolytic action in the light/dark test was not flumazenil-sensitive and there was no rebound anxiogenic effect on withdrawal from chronic VA21B7 treatment for 15 consecutive days. Moreover, VA21B7 was not amnesic like the benzodiazepines but low doses of 2-4 mg/kg

reduced the memory deficits induced in rats by scopolamine. Much higher doses were necessary to decrease spontaneous motor activity in rats. Since VA21B7 appears to be well tolerated in rodents at high doses, we think that it is of potential interest as an anxiolytic in humans.

*Benzimidazolones, benzimidazoles and other imidazoles*

The common chemical structure of a benzimidazolone is:



- Iodophenpropit (4-(1H-imidazol-4-yl-methyl)-piperidine)
  - BIMU 1 (endo-N-(8-methyl-8-azabicyclo[3.2.1.]oct-3-yl)-2,3-dihydro-3-ethyl-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride)
  - 2-piperazin-benzimidazole
  - 2-piperidin-benzimidazole
  - Cilansetron (1-10-[(2-methyl-1H-imidazol-1-yl)methyl]-5,6,8,9,10,11-hexahydro-4H-pyrido [3,2,1-jk]carbazol-11-one hydrochloride)
  - GK 128 (2-[(2-methylimidazol-1-yl)methyl]benzo[i]-thiochromen-1-one monohydrochloride hemihydrate)
- Effect of a novel 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>) receptor antagonist, GK-128, on 5-HT<sub>3</sub> receptors mediating contractions and relaxations in guinea-pig distal colon.

Ito C, Kawamura R, Isobe Y, Tsuchida K, Muramatsu M,  
Higuchi S;

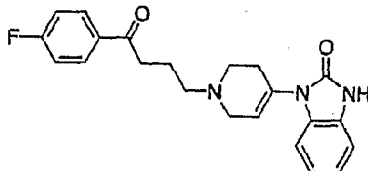
Gen Pharmacol 1997 Sep, 29:3:353-9

5 We investigated 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>)  
receptor-mediating contractions and relaxations in  
the guinea-pig isolated distal colon using various  
5-HT<sub>3</sub> receptor agonists and antagonists, including  
10 GK-128 (2-[(2-methylimidazol-1-yl) methyl] benzo[f]  
thiochromen-1-one monohydrochloride hemihydrate).  
2. Selective 5-HT<sub>3</sub> receptor agonists, 2-methyl-5-HT  
and m-chlorophenylbiguanide, produced spantide-  
insensitive contraction and atropine-insensitive  
contraction and the relaxation. These agonists  
15 showed a small, but significant, difference of  
potency between contraction and relaxation. 3. GK-  
128 competitively blocked both 2-methyl-5-HT- and m-  
chlorophenylbiguanide-induced responses with similar  
potency. The affinities of GK-128 for spantide-  
20 insensitive contraction and atropine-insensitive  
contraction were ten-fold higher than for  
relaxation. 4. Other selective 5-HT<sub>3</sub> receptor  
antagonists, azasetron and tropisetron, also  
exhibited higher affinity in contraction than in  
25 relaxation, but the extent of their affinity  
differences was smaller than that observed in GK-  
128. In contrast, granisetron, ramosetron and  
ondansetron exhibited no significant differences in  
their affinity values among the three responses. 5.  
30 These results suggest that the 5-HT<sub>3</sub> receptors which  
mediate contraction and relaxation in the guinea-pig  
distal colon may not be the same, and that GK-128 is  
a 5-HT<sub>3</sub> receptor antagonist with a stronger potency  
for contraction.

- Droperidol. Ingår i Dridol, Janssen-Cilag

**Droperidolum INN (Droperidol)**

1-[1-(3-(4-Fluorobenzoyl)propyl)-1,2,3,6-tetrahydro-4-pyridyl]-1,3-dihydro-2H-benzimidazol-2-on



- KAE-393/YM-114

((R)-5-[(2,3-dihydro-1-indolyl)carbonyl]-4,5,6,7-tetrahydro-1H-benzimidazole

Comparison of the effects of trimebutine and YM114 (KAE-393), a novel 5-HT<sub>3</sub> receptor antagonist, on stress-induced defecation. Miyata K, Ito H, Yamano M, Hidaka K, Kamato T, Nishida A, Yuki H; *Eur J Pharmacol* 1993 Dec 7, 250:2:303-10

YM114 (KAE-393), (R)-5-[(2,3-dihydro-1-indolyl)-carbonyl]-4,5,6,7-tetrahydro-1H-benzimidazole hydrochloride, is a derivative of YM060, a potent 5-HT<sub>3</sub> receptor antagonist. We investigated the effects of YM114 on 5-HT<sub>3</sub> receptors, both in vitro and in vivo, and on bowel dysfunction induced by restraint stress, 5-HT and thyrotropin-releasing hormone (TRH), and compared them with the effect of trimebutine. YM114 dose dependently inhibited the reduction in heart rate induced by 5-HT (30 micrograms/kg i.v.) in rats (ED<sub>50</sub> = 0.31 micrograms/kg i.v.), and the potency of YM114 was almost the same as that of the racemate. The S-form

of YM114 also inhibited 5-HT-induced bradycardia, but 1350 times less potent than the R-form. YM114 and its S-form inhibited [3H]GR65630 binding to N1E-115 cell membranes in a concentration-dependent manner with  $K_i$  values of 0.341 and 616 nM, respectively, showing the isomeric activity ratio (R-/S-form) of YM114 to be much greater (1800). YM114 antagonized 5-HT-induced depolarization of the nodose ganglion ( $EC_{50}$  = 1.39 nM). Trimebutine (1 mg/kg i.v.) failed to inhibit 5-HT-induced bradycardia, implying that it does not possess 5-HT<sub>3</sub> receptor antagonistic activity. YM114 significantly and dose dependently prevented restraint stress-, 5-HT- and TRH-induced increases in fecal pellet output, and restraint stress- and 5-HT-induced diarrhea in rats and mice ( $ED_{50}$  = 6.9, 72.5, 154.6, 9.7 and 52.4 micrograms/kg p.o., respectively). Trimebutine significantly prevented stress- and 5-HT-induced diarrhea ( $ED_{50}$  = 29.4 and 87.3 mg/kg p.o., respectively), but only partially affected stress-, 5-HT- and TRH-induced increases in fecal pellet output. Thus, YM114 is a potent and stereoselective 5-HT<sub>3</sub> receptor antagonist with much greater protective effects against stress-induced defecation than trimebutine.hydrochloride).

- Itasetron=DAU6215 ((3- $\alpha$ -tropanyl)1H-benzimidazolone-3-carboxamide chloride) Intravenous itasetron: establishing the effective dose range for the prophylactic control of acute emesis in cancer patients undergoing high-dose cisplatin chemotherapy., Patoia L, Del Favero A, Giglietti A, Malacarne P, Donati D, Indelli M, Bensi G, Palladino MA, Cigarini P, Kempe R, Voigt T; *Clin Oncol* (R Coll Radiol) 1999, 11:2:99-104



Nausea and vomiting induced by chemotherapy are a major cause of distress to patients and reduce compliance with potentially beneficial treatment. Itasetron hydrochloride is a new 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>) antagonist with potent antiemetic properties. It is more potent than ondansetron in animal models and in early clinical studies it demonstrates a long half-life and does not undergo hepatic biotransformation before elimination. The aim of this open, uncontrolled study was to establish the effective dose range of itasetron hydrochloride given intravenously (i.v.) to patients due to receive high-dose cisplatin chemotherapy (50-120 mg/m<sup>2</sup>) for the first time. Thirty-nine patients were enrolled in the trial and received a single i.v. infusion of itasetron hydrochloride at a dose of 17-280 microg/kg body weight before commencing the cisplatin infusion (median dose 90-110 mg/m<sup>2</sup>). Antiemetic protection was demonstrated by doses in the range of 35-280 microg/kg. The 17 microg/kg dose was not effective. Treatment failure (>5 emetic episodes/24 hours) was reported in only six (16%) of the 38 evaluable patients over all treatment groups. Adverse events were generally mild or moderate and of a similar type and incidence to those of current 5-HT<sub>3</sub> antagonists. Physicians' and patients' assessments of efficacy and tolerability of itasetron hydrochloride were similar, the majority rating the treatment as 'good' or 'very good'. In conclusion, itasetron hydrochloride is effective in the dose range 35-280 microg/kg in preventing cisplatin-induced emesis. Taken together with results from a larger dose-finding study, a dose corresponding to 35 microg/kg (equivalent to 2.5 mg itasetron, calculated as free base) has been pursued in Phase III studies with the i.v. formulation.

- Lerisetron

5 New 2-piperazinybenzimidazole derivatives as 5-HT<sub>3</sub> antagonists. Synthesis and pharmacological evaluation. Orjales A, Mosquera R, Labeaga L, Rodés R

J Med Chem 1997 Feb 14, 40:4:586-93

10 A series of 2-piperazinybenzimidazole derivatives were prepared and evaluated as 5-HT<sub>3</sub> receptor antagonists. Their 5-HT<sub>3</sub> receptor affinities were evaluated by radioligand binding assays, and their abilities to inhibit the 5-HT-induced Bezold-Jarisch  
15 reflex in anesthetized rats were determined. Compound 7e (lerisetron, pK<sub>i</sub> = 9.2) exhibited higher affinity for the 5-HT<sub>3</sub> receptor than did tropisetron and granisetron, while compound 7q (pK<sub>i</sub> = 7.5) had very low affinity for this receptor, showing that  
20 substitution on the N1 atom of the benzimidazole ring is essential for affinity and activity. The effect of substitution on the aromatic ring of benzimidazole by several substituents in different positions is also discussed. A strong correlation  
25 between the 5-HT<sub>3</sub> antagonistic activity of the studied compounds and the position of substitution on the aromatic ring was established. Thus, while the 4-methoxy derivative 7m showed weak affinity for the 5-HT<sub>3</sub> receptor (pK<sub>i</sub> = 6.7), the 7-methoxy  
30 derivative 7n exhibited the highest affinity (pK<sub>i</sub> = 9.4). Compounds 7e and 7n are now under further investigation as drugs for the treatment of nausea and emesis evoked by cancer chemotherapy and radiation.

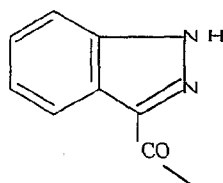
35

- Lurosetron

- Mirisetron =WAY100579
- Ramosetron =YM 060. [(R)-5-[(1-methyl-3-indolyl)-  
carbonyl]-4,5,6,7-tetrahydro-1H-benzimidazole  
hydrochloride]

#### *Indazole carboxamide derivatives*

The compounds have the general structure.



- AS5370 ((+/-)-N-[1-methyl-4-(3-methyl-benzyl)-  
hexahydro-1H-1,4-diazepin-6-yl]-1H-indazole-3-  
carboxamide dihydrochloride). The compound is also a  
diazepin derivative.

- DAT582 (the compound is the R- enantimer of compound  
AS5370) 5-HT3 receptor antagonist effects of DAT-  
582, (R) enantiomer of AS-5370.

Yoshida N, Omoya H, Kato S, Ito T, Eur J Pharmacol,  
1992 Jun 17, 216:3:435-40

The serotonin 5-HT3 receptor antagonist effects of  
DAT-582, the (R) enantiomer of AS-5370 ((+/-)-N-[1-  
methyl-4-(3-methyl-benzyl)hexahydro-1H-1,4-diazepin-  
6-yl]-1H-indazole-3-carboxamide dihydrochloride),  
and its antipode were compared with those of AS-5370  
and existing 5-HT3 receptor antagonists. In  
anesthetized rats, DAT-582 antagonized 2-methyl-5-  
HT-induced bradycardia with an ED50 value of 0.25  
microgram/kg i.v., whereas the (S) enantiomer was  
without effect even at 1000 micrograms/kg i.v. In

antagonizing the bradycardia, DAT-582 was as potent as granisetron, slightly more potent than AS-5370, and 2, 5 and 18 times more potent than ondansetron, ICS 205-903 and renzapride, respectively, although it was less potent than zacopride. DAT-582 inhibited cisplatin (10 mg/kg i.v.)-induced emesis in ferrets with an ED50 value of 3.2 micrograms/kg i.v. twice. The antiemetic activity of DAT-582 was more potent than that of the existing 5-HT3 receptor antagonists examined, except zacopride. In contrast, the (S) enantiomer had little effect at 1000 micrograms/kg i.v. twice. In isolated guinea-pig ileum, DAT-582 inhibited 5-HT-induced contractions with an IC50 value of 91 nM, whereas the (S) enantiomer hardly inhibited them even at 1000 nM. These results suggest that DAT-582, the (R) enantiomer of AS-5370, potently and selectively blocks 5-HT3 receptors.

- N-3389 (N-3389 (endo-3,9-dimethyl-3,9-diazabicyclo[3,3,1]non-7-yl 1H-indazole-3-carboxamide dihydrochloride)

Antagonistic activities of N-3389, a newly synthesized diazabicyclo derivative, at 5-HT3 and 5-HT4 receptors., Hagihara K, Hayakawa T, Arai T, Eguchi H, Mino S, Kawase S, Eur J Pharmacol 1994 Dec 12, 271:1:159-66

The antagonistic activities of compound N-3389 (endo-3,9-dimethyl-3,9-diazabicyclo[3,3,1]non-7-yl 1H-indazole-3-carboxamide dihydrochloride) at 5-HT3 and 5-HT4 receptors were examined using in vitro and in vivo assays. N-3389 showed potent 5-HT3 receptor antagonistic activities in a radioligand binding assay ( $pK_i = 8.77$ ), against 2-methyl-5-HT (2-Me-5-HT)-induced bradycardia in rats (ED50 = 0.73 micrograms/kg i.v., 38 micrograms/kg p.o.) and

against 2-Me-5-HT-induced contraction in longitudinal muscle myenteric plexus preparations of guinea-pig ileum. ( $IC_{50} = 3.2 \times 10^{-8}$  M). As a preliminary to investigating the effect of N-3389 on 5-HT<sub>4</sub> receptors, we examined the contraction induced by 5-HT in guinea-pig ileum preparations. We confirmed that 5-HT ( $10^{-8}$ - $10^{-5}$  M) induced biphasic contractions in the preparations.

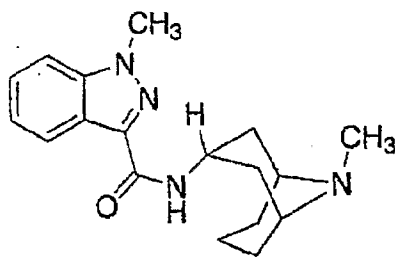
Furthermore, 5-HT<sub>3</sub> receptor antagonism inhibited the late phase of the contraction induced by high concentrations of 5-HT ( $3 \times 10^{-6}$ - $10^{-5}$  M), whereas 5-HT<sub>4</sub> receptor antagonism inhibited the early phase of the contraction induced by low concentrations of 5-HT ( $10^{-8}$ - $10^{-6}$  M). N-3389 ( $10^{-7}$ - $10^{-5}$  M) inhibited both phases of contraction induced by 5-HT. In addition, N-3389 ( $3 \times 10^{-7}$ - $3 \times$

$10^{-6}$  M) was found to inhibit the increase of electrically stimulated twitch responses induced by 5-HT ( $10^{-8}$  M) longitudinal muscle myenteric plexus preparation of the guinea-pig ileum. These results suggest that N-3389 acts as a 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptor antagonist.

- BRL 43694=Kytril® =Granisetron

#### Granisetronum INN (Granisetron)

1-Metyl-N-(endo-9-metyl-9-azabicyklo[3.3.1]non-3-yl)-1H-indazol-3-karboxamid



Selective and functional 5-hydroxytryptamine<sub>3</sub> receptor antagonism by BRL 43694 (granisetron).; Sanger GJ, Nelson DR Eur J Pharmacol 1989 Jan 10, 159:2:113-24

5 The activity of BRL 43694 (granisetron) was investigated using established models of 5-HT<sub>3</sub> receptor activity. In guinea-pig isolated ileum, BRL 43694 antagonised the contractions evoked by  
10 relatively high concentrations of 5-HT ( $pA_2 = 8.1 \pm 0.2$ ). However, except in high concentrations, BRL 43694 did not affect the contractions of similar preparations of ileum, evoked by electrical field stimulation (cholinergically mediated), the  
15 nicotinic agonist dimethylphenyl piperazinium (DMPP) or by cholecystokinin octapeptide. Similarly, BRL 43694 did not affect electrically evoked, cholinergically mediated contractions of rat or human isolated stomach. In other models of 5-HT<sub>3</sub>  
20 receptor activity (rabbit isolated heart, Bezold-Jarisch reflex in anaesthetised rats), potent antagonism by BRL 43694 was demonstrated. In radioligand binding studies on rat brain membranes, BRL 43694 had little or no affinity for 5-HT<sub>1A</sub>, 5-  
25 HT<sub>1B</sub>, 5-HT<sub>2</sub> or for many other binding sites. BRL 43694 may therefore be a potent and selective 5-HT<sub>3</sub> receptor antagonist.

• Litoxetine=SL81.0385

30 Litoxetine: a selective 5-HT uptake inhibitor with concomitant 5-HT<sub>3</sub> receptor antagonist and antiemetic properties. Angel I, Schoemaker H, Prouteau M, Garreau M, Langer SZ.; Eur J Pharmacol 1993 Mar 2, 232:2-3:139-45  
35

The selective 5HT uptake inhibitor, litoxetine (SL 81.0385), currently under development as an antidepressant was shown to have antiemetic properties in the ferret. Litoxetine (at 1 and 10 mg/kg i.v.) dose dependently reduced the number of retches and vomiting as well as the number of emetic episodes induced by cisplatin (10 mg/kg i.v.) and delayed the onset of emesis. Fluoxetine (at 1 or 10 mg/kg i.v.) failed to inhibit cisplatin-induced emetic responses and, in contrast, significantly increased the number of retches and vomiting and accelerated the onset of emesis. The possibility that the antiemetic effects of litoxetine may be mediated through an interaction with 5HT<sub>3</sub> receptors was studied using [3H]quipazine or [3H]BRL 43694 to label the 5HT<sub>3</sub> receptor. Litoxetine has moderate affinity for cerebral 5HT<sub>3</sub> receptors ( $K_i = 85$  nM), while fluoxetine, similar to other 5HT uptake inhibitors, has only negligible affinity for this receptor ( $K_i = 6.5$  microm). It is proposed that litoxetine inhibits cisplatin-induced emetic responses due to its moderate 5HT<sub>3</sub> antagonist properties. The clinical use of the majority of serotonergic antidepressants (e.g. fluoxetine, fluvoxamine etc.) is associated with gastrointestinal discomfort (particularly nausea and vomiting) as a major side-effect. If nausea and vomiting associated with the use of 5 HT uptake inhibitors are due to stimulation of 5HT<sub>3</sub> receptors, the concomitant 5HT<sub>3</sub> antagonism of litoxetine may limit the gastrointestinal side-effects of this novel antidepressant and thus offer an important advantage.

- LY 278584 ((1-methyl-N-(8-methyl-8-azabicyclo-[3.2.1.]oct-3-yl)-1H-indazole-3-carboxamide)

Specific [3H]LY278584 binding to 5-HT<sub>3</sub> recognition sites in rat cerebral cortex.

Wong DT, Robertson DW, Reid LR; *Eur J Pharmacol* 1989 Jul 4, 166:1:107-10

5

Binding of [3H]LY278584 a 1-methyl-indazole-carboxamide, to putative 5-HT<sub>3</sub> recognition sites in membranes isolated from cerebral cortex of rat brain, is examined. Specific binding of [3H]LY278584 accounts for 83-93% of total binding. The unlabelled LY278584 has 500 times greater affinity for [3H]LY278584 recognition sites than its 2-methyl analogue (LY278989), and their potencies parallel their antagonism of the peripheral 5-HT<sub>3</sub> receptors. Moreover, the order of potencies of other known antagonists of 5-HT<sub>3</sub> receptors supports the conclusion that [3H]LY278584 binds to putative 5-HT<sub>3</sub> receptors in cortical membranes.

20

- LY-278,584 maleate, see above.

- LY258-458

- LY 278989

25

Specific [3H]LY278584 binding to 5-HT<sub>3</sub> recognition sites in rat cerebral cortex.

Wong DT, Robertson DW, Reid LR; *Eur J Pharmacol* 1989 Jul 4, 166:1:107-10

30

Binding of [3H]LY278584 a 1-methyl-indazole-carboxamide, to putative 5-HT<sub>3</sub> recognition sites in membranes isolated from cerebral cortex of rat brain, is examined. Specific binding of [3H]LY278584 accounts for 83-93% of total binding. The unlabelled LY278584 has 500 times greater affinity for [3H]LY278584 recognition sites than its 2-methyl analogue (LY278989), and their potencies parallel

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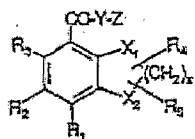


their antagonism of the peripheral 5-HT<sub>3</sub> receptors. Moreover, the order of potencies of other known antagonists of 5-HT<sub>3</sub> receptors supports the conclusion that [3H]LY278584 binds to putative 5-HT<sub>3</sub> receptors in cortical membranes.

- LY-211-000

*Benzofuranes, benzooxazines, benzo(di)azepines, bensothiazepines*

A general structure for these classes of compounds is:



- 2,3-dihydro-benzofuran-7-carboxamides. X<sub>1</sub>=C, X<sub>2</sub>=O; five-membered ring system.
- RG 12915 ([4-[N-(1-azabicyclo[2.2.2.]octan-3-(S)-yl)]2-chloro-cis 5a-(S)-9a-(S)-5a,6,7,8,9,9a-hexahydrobenzofurancarboxamide hydrochloride])
- ADR 851 [4-amino-5-chloro-2,3-dihydro-N-(pyrrolidin-2-ylmethyl)benzofuran-7-carboxamide]

- ADR-882

Analgesic effects of S and R isomers of the novel 5-HT<sub>3</sub> receptor antagonists ADR-851 and ADR-882 in rats.; Sufka KJ, Giordano J, *Eur J Pharmacol* 1991 Oct 29, 204:1:117-9

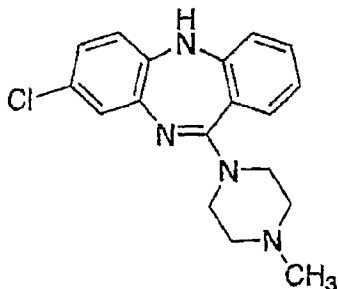
The present study examined analgesia produced by S and R isomers of the novel 5-HT<sub>3</sub> receptor antagonists, ADR-851 and ADR-882 (0.1-10 mg/kg s.c.) against acute thermal, mechanical and formalin-induced inflammatory pain in rats. Neither isomer of ADR-851 or ADR-882 was analgesic in the thermal or mechanical test. Similarly, neither S or R forms of ADR-882 produced significant anti-nociception in the formalin test. In contrast, ADR-851R produced significant analgesia at 3 and 10 mg/kg doses in this test, while ADR-851S produced significant analgesia only at 1 mg/kg.

- RP 62203 (2-[3-(4-(4-fluorophenyl)-piperazinyl)-propyl]naphto[1,8- ca]isothiazole-1,1-dioxide)

- Clozapine. Ingår i Leponex, Novartis

**Clozapinum INN (Klozapin)**

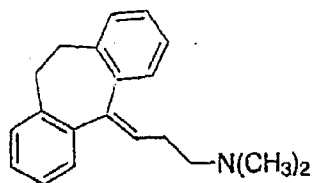
8-Kloro-11-(4-metyl-1-piperaziny)-5H-dibenso[b,e][1,4]diazepin



- Amitriptyline

**Amitriptylinum INN (Amitriptylin)**

5-(3-Dimetylaminoethyliden)-10,11-dihydro-5H-dibens[a,d]cyklohepten



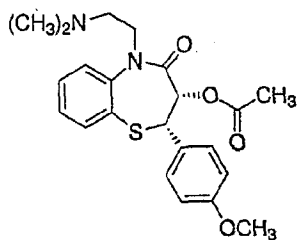
- Cyproheptadine. Is the active ingredient of Periactin, MSD

5

- Diltiazem  
Is the active ingredient in Cardizem, Pharmacia Corporation

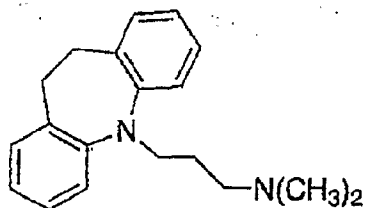
**Diltiazemum INN (Diltiazem)**

(2S,3S)-3-(Acetyloxi)-5-[2-(dimetylamino)etyl]-2-(4-metoxifenyl)-2,3-dihydro-1,5-benzotiazepin-4(5H)-on

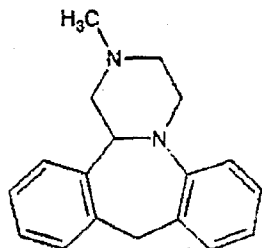


- Imipramin

5-(3-Dimethylaminopropyl)-10,11-dihydro-5H-dibenzo[*b,f*]azepin



- Mianserin

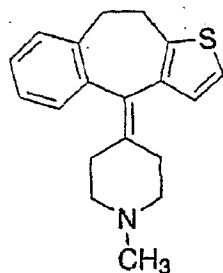


5

- Mirtazapine (1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a] pyrido [2,3-c] benzazepine)
- Pizotifen

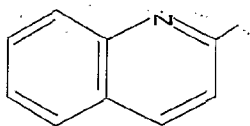
**Pizotifenum INN (Pizotifen)**

4-(1-Metyl-4-piperidyliden)-9,10-dihydro-4H-benzo-[4,5]cyklohepta[1,2-*b*]tiofen



*Quinolines, quinolicines and isoquinolines*

The common structure of quinoline is:



5 Isoquinoline and quinolizine are isomers of quinoline.

- Quinoline-3-carboxamides
- Quinoline-4-carboxylates
- 10 • Isoquinoline-1-one (isomer till quinolin-1-one)
- SEC 579
- 15 • RS 56532 ( (S)-6-amino-5-chloro-2-(1-azabicyclo-[2, 2, 2]octan-3-yl) 2,3-dihydro-1H-benz[de]-isoquinoline-1,3-dione hydrochloride)
- 3-(1-piperazinyl)-2-quinoxalinecarbonitrile
- 20 • 3-(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile
- KF 17643 (endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl-2-(n-propyloxy)-4-quinolinecarboxylate)
- 25 • KF 18259 ((endo-(8-methyl-8-aza- bicyclo[3.2.1]oct-3-yl)-1-isobutyl-2-oxo-1,2-dihydro-4-quinoline-carboxylate hydrochloride)
- 30 • KF 20170 (endo-N-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-4-hydroxy-3- quinolinecarboxamide

- Palonosetron=RS 25259-197  
(3aS)-2-[(S)-1-azabicyclo[2.2.2]oct-3-yl]-  
2,3,3a,4,5,6-hexahydro- 1- oxo-1H-benzo[de]-  
5 isoquinoline-hydrochloride
- Quipazine (2-(1-piperazinyl)-Quinoline)
- N-metylquipazin
- 10 • 4-Ph-N-Me-quipazine
- RS-42358-197 [(S)-N-(1-azabicyclo[2.2.2]oct-3-yl)-  
2,4,5,6-tetrahydro-1 H-benzo[de]isoquinolin-1-one  
15 hydrochloride]
- RS-056812-198 (R)-N-(quinuclidin-3-yl)-2-(1-methyl-  
1 H-indol-3-yl)-2-oxo-acetamide
- 20 • RS-25259-197 [(3aS)-2-[(S)-1-azabicyclo[2.2.2]oct-3-  
yl]-2,3,3a,4,5,6-hexahydro- 1- oxo-1H-benzo[de]-  
isoquinoline-hydrochloride)

25 The interaction of RS 25259-197, a potent and  
selective antagonist, with 5-HT<sub>3</sub> receptors, in  
vitro. Wong EH, Clark R, Leung E, Loury D, Bonhaus  
DW, Jakeman L, Parnes H, Whiting RL, Eglen RM, Br J  
Pharmacol 1995 Feb, 114:4:851-9

30 A series of isoquinolines have been identified as 5-  
HT<sub>3</sub> receptor antagonists. One of these, RS 25259-197  
[(3aS)-2-[(S)-1-azabicyclo[2.2.2]oct-3-yl]-  
2,3,3a,4,5,6-hexahydro- 1- oxo-1H-benzo[de]iso-  
quinoline-hydrochloride], has two chiral centres.  
35 The remaining three enantiomers are denoted as  
RS 25259-198 (R,R), RS 25233-197 (S,R) and RS 25233-  
198 (R,S). 2. At 5-HT<sub>3</sub> receptors mediating

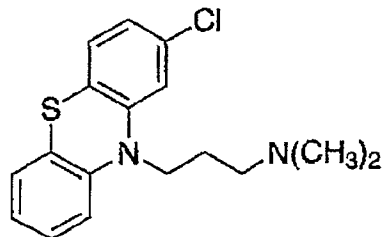
contraction of guinea-pig isolated ileum, RS 25259-197 antagonized contractile responses to 5-HT in an unsurmountable fashion and the apparent affinity (pKB), estimated at 10 nM, was  $8.8 \pm 0.2$ . In this tissue, the  $-\log KB$  values for the other three enantiomers were  $6.7 \pm 0.3$  (R,R),  $6.7 \pm 0.1$  (S,R) and  $7.4 \pm 0.1$  (R,S), respectively. The apparent affinities of RS 25259-197 and RS 25259-198, RS 25233-197 and RS 25233-198 at 5-HT<sub>3</sub> receptors in membranes from NG-108-15 cells were evaluated by a [3H]-quipazine binding assay. The  $-\log K_i$  values were  $10.5 \pm 0.2$ ,  $8.4 \pm 0.1$ ,  $8.6 \pm 0.1$  and  $9.5 \pm 0.1$ , respectively, with Hill coefficients not significantly different from unity. Thus, at these 5-HT<sub>3</sub> receptors, the rank order of apparent affinities was (S,S) > (R,S) > (S,R) = (R,R). 3. RS 25259-197 displaced the binding of the selective 5-HT<sub>3</sub> receptor ligand, [3H]-RS 42358-197, in membranes from NG-108-15 cells, rat cerebral cortex, rabbit ileal myenteric plexus and guinea-pig ileal myenteric plexus, with affinity (pK<sub>i</sub>) values of  $10.1 \pm 0.1$ ,  $10.2 \pm 0.1$ ,  $10.1 \pm 0.1$  and  $8.3 \pm 0.2$ , respectively.

## Phenthiazines and Benzoxazines

- Chlorpromazine

**Chlorpromazinum INN (Klorpromazin)**

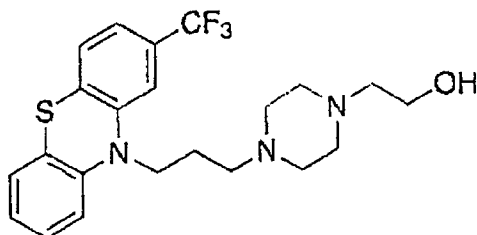
**10-(3-Dimethylaminopropyl)-2-klorofentiazin**



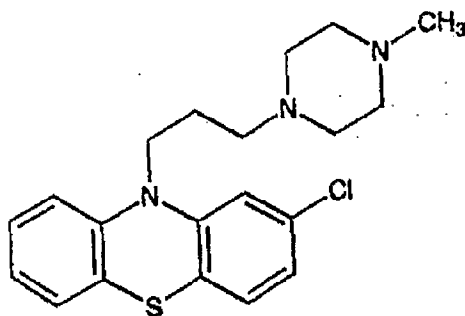
- Cyamemazine (10-(3-Dimethylamino-2-methylpropyl)phenothiazine-2-carbonitrile)
- Fluphenazin

**Fluphenazinum INN (Flufenazin)**

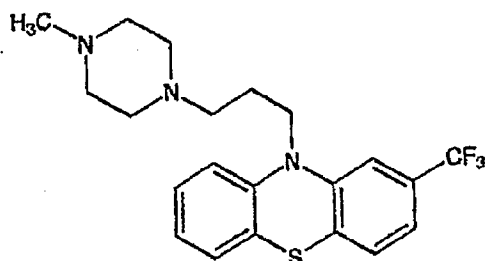
10-[3-(4-(2-Hydroxyethyl)-1-piperazinyl)propyl]-2-trifluoromethylfentiazin



- 5 • Prochlorperazine=Stemetil



- 10 • KB-6933 (6-amino-5-chloro-1-isopropyl-2-(4-methyl-1-piperazinyl)benzimidazole dimaleate)
- Perfenazine. Ingår i Trilafon. Cl istället för CF<sub>3</sub> i formeln för Flufenazine
- Trifluoperazine





- Azasetron=Y25130 (+/-)-N-(1-azabicyclo[2.2.2]oct-3-yl)-6-chloro-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-8-carboxamide monohydrochloride

Pharmacokinetics of azasetron (Serotone), a selective 5-HT<sub>3</sub> receptor antagonist.

Tsukagoshi S Gan To Kagaku Ryoho 1999 Jun, 26:7:1001-8

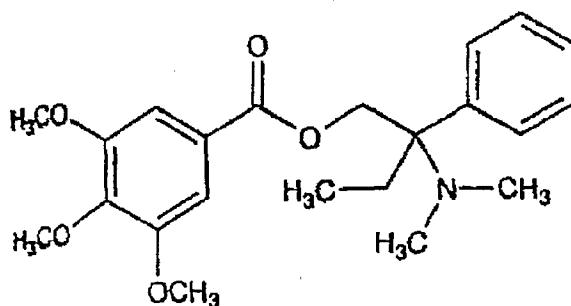
5-HT<sub>3</sub> receptor antagonists have been established in a number of clinical trials as effective agents in the management of nausea and vomiting induced by cancer chemotherapy including cisplatin. Azasetron (Serotone) is a potent and selective 5-HT<sub>3</sub> receptor antagonist, and classified as benzamide derivative. It has a different chemical structure from indole-type 5-HT<sub>3</sub> receptor antagonists such as granisetron, ondansetron, ramosetron and tropisetron. The major difference is found in the pharmacokinetic profiles. Approximately 60-70% of azasetron administered i.v. and orally is excreted in urine as the unmetabolized form. Also, orally-administered azasetron has shown to be absorbed and/or secreted by the saturable transport mechanism in the small intestine, resulting in good bioavailability as approximately 90%. In this report, the relationship between the structure of 5-HT<sub>3</sub> receptor antagonists (especially azasetron) and their pharmacokinetics were described.

- 5-((Dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazole

- 1,4-Benzoxazin-8-Carboxamide

Other compounds, including piperidines, piperazines, alkaloides, benzoates and ureas

- Anpirtoline (6-Chloro-2-[piperidinyl-4-thio]-pyridine)
- 5 • Ritanserine
- NAN-190 (1-(2-methoxyphenyl)-4-[4-(2-phthalimido)-butyl] piperazine)
- Naphtimides.
- 10 • TFMPP (1-(3-trifluoromethylphenyl)piperazine)
- Ifenprodil (dl-erythro-4-benzyl-alpha-(4-hydroxyphenyl)-beta-methyl-1-piperidine-ethanol tartrate) (ifenprodil tartrate)
- 15 • MCPP (Meta-chlorophenylpiperazine) (mCPP)
- MK-212 (6-chloro-2-[1-piperazinyl]-pyrazine)
- Metergoline ([[(8{BETA})-1,6-dimethylergolin-8-yl]methyl]-Carbamic acid phenylmethyl ester)
- 20 • Methysergide (1-methyl-D-lysergic acid butanolamide)
- S-apomorfin
- 25 • Tropanyl-3,5-dimethylbenzoate
- Trimebutine, ett 3,4,5-trimetoxybenzoate derivat.



- TMB-8 (8-(N,N-diethylamino)octyl 3,4,5-trimethoxybenzoate)

- 5 • Phenylbiguanide

Functional characterization of a 5-HT<sub>3</sub> receptor which modulates the release of 5-HT in the guinea-pig brain., Blier P, Bouchard C Br J Pharmacol 1993 Jan, 108:1:13-22

10 The aims of the present study were to confirm the modulation by 5-HT<sub>3</sub> receptors of the electrically evoked release of tritium from slices preloaded with [3H]-5-HT of guinea-pig frontal cortex, hippocampus and hypothalamus, and to assess their functional role in 5-HT release. 2. The selective 5-HT<sub>3</sub> agonist, 2-methyl-5-HT, introduced 8 min before the electrical stimulation, enhanced in a concentration-dependent manner the evoked release of [3H]-5-HT in the three brain regions studied. The 5-HT<sub>3</sub> agonists, phenylbiguanide and m-chlorophenyl-biguanide, did not enhance the release of tritium in frontal cortex and hypothalamus slices. 3. In hypothalamus slices, this response was lost when 2-methyl-5-HT was introduced 20 min before the stimulation, thus indicating that these 5-HT<sub>3</sub> receptors desensitize rapidly. When 2-methyl-5-HT was added 20-min before the first stimulation period to desensitize the 5-HT<sub>3</sub> receptors, removed for 24 min, and then re-introduced 8 min before the second stimulation period, the enhancing effect of 2-methyl-5-HT was restored, thus indicating that these 5-HT<sub>3</sub> receptors can rapidly regain normal sensitivity. 4. The enhancing effect of 2-methyl-5-HT was attenuated by the 5-HT<sub>3</sub> receptor antagonists m-chlorophenylpiperazine = quipazine = ondansetron > or =

ICS 205-930 = BRL 24924 > MDL 72222 = zacopride. 5. The 5-HT reuptake blocker, paroxetine, enhanced the electrically evoked release of tritium when introduced 8 min before stimulation; this effect of paroxetine was blocked by ICS 205-930, thus indicating that these 5-HT<sub>3</sub> receptors can be activated by endogenous 5-HT. 6. In the absence of electrical stimulation, 2-methyl-5-HT (10 micromM) produced a marked enhancement of the basal release of [3H]-5-HT which was calcium-dependent and blocked by S-zacopride but not by paroxetine. 7. The enhancing effect of 2-methyl-5-HT was dependent both on the frequency of stimulation, as indicated by the attenuated effect of 120 stimulations delivered at 1 Hz instead of 5 Hz, and on the duration of the stimulation, as indicated by the more pronounced effect of pulses delivered at 5 Hz for 24 s instead of 72 s or 120 s. McNeil-A-343 (4-(m-chlorophenyl-carbamoyloxy)-2-butynyl-trimethylammonium chloride).

- MDL 72222 (1 alpha H, 3 alpha, 5 alpha H-tropan-3-yl-3,5-dichlorobenzoate)

MDL 72222: a potent and highly selective antagonist at neuronal 5-hydroxytryptamine receptors., Fozard JR Naunyn Schmiedebergs Arch Pharmacol 1984 May, 326:1:36-44

The properties of MDL 72222 (1 alpha H, 3 alpha, 5 alpha H-tropan-3-yl-3,5-dichlorobenzoate), a novel compound with potent and selective blocking actions at certain excitatory 5-hydroxytryptamine (5-HT) receptors on mammalian peripheral neurones, are described. On the rabbit isolated heart, MDL 72222 was a potent antagonist of responses mediated through the receptors for 5-HT present on the terminal sympathetic fibres. The threshold for

antagonism was approximately 0.1 nM and the negative logarithm of the molar concentration of MDL 72222, which reduced the chronotropic response of the isolated rabbit heart to twice an ED50 of 5-HT to that of the ED50 was 9.27. MDL 72222 was also highly selective since responses to the nicotine receptor agonist, dimethylphenylpiperazinum iodine (DMPP), were inhibited only at concentrations more than 1000 times those necessary to inhibit 5-HT. In the anaesthetized rat, MDL 72222 produced marked blockade of the Bezold-Jarisch effect of 5-HT. Again, inhibition was selective since much higher doses of MDL 72222 failed to alter the response to electrical stimulation of the efferent vagus nerves. In contrast, MDL 72222 proved only a weak and essentially non-selective antagonist of responses mediated by the 5-HT M-receptor present on the cholinergic nerves of the guinea-pig ileum. MDL 72222 does not block smooth muscle contractile responses elicited by oxytocin or mediated through 5-HT D-receptors, muscarinic or nicotinic cholinceptors or histamine H1-receptors except at relatively high concentrations.

• MDL 72699 MDL 72699 är kvartenära saltet av MDL 72222.

• Mepyramine (N,N-dimethyl N'-(methoxy-4 benzyl)-N'-(pyridyl-2)ethylenediamine).

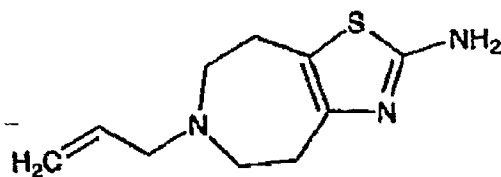
• Galanolactone= Gingerol

The irregularly shaped roots (rhizomes) of ginger (*zingiber officinale*) are used extensively in Chinese, Indian, and Japanese cultures where they are believed to have anti-inflammatory, analgesic, cholesterol-lowering, and antithrombotic properties. Although ginger has been evaluated for the

treatment of nausea and vomiting associated with hyperemesis gravidarum, anesthesia, and chemotherapy, this review will focus on ginger for motion sickness.

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- Talipexole



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## Additional compounds

- 5     • YM 26103-2  
      • YM 26308-2  
      • M-840 ([3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazol-5-yl]-methyl]trimethyl-ammonium iodide)

Ref. A mechanism of 5-HT<sub>3</sub> receptor mediation is  
10     involved etiologically in the psychological stress  
      lesion the stomach of the mouse. , J Pharmacol Exp  
      Ther, 1994 Oct, 271:1, 100-6

The role of brain amines, possibly involved in  
15     psychological stress, was evaluated and we postulate  
      that the 5-hydroxytryptamine 5-HT<sub>3</sub> receptors in the  
      central nervous system are involved in the gastric  
      lesion formation by psychological stress. The stress  
      was in a communication box paradigm, in which each  
20     nonshocked mouse (responder) was placed in a Plexi-  
      glas compartment adjacent to mice receiving  
      electrical shocks (sender). The responder mice  
      revealed rather depressed gastric secretion, but  
      developed gastric lesions which are significantly  
25     attenuated by pretreatment of dl-p-  
      chlorophenylalanine methyl ester:HCl (PCPA; 200-400  
      mg/kg p.o.), but not 6-hydroxydopamine (6-OH-DA; 60  
      micrograms/body i.c.v. or 80 mg/kg i.p. 1 hr after a  
      20-mg/kg i.p. dose of desipramine). Oral treatment  
30     with GR38032F (0.01-1 mg/kg), ICS205-930 (0.01-20  
      mg/kg), MDL72222 (0.01-1 mg/kg), metoclopramide  
      (0.1-100 mg/kg), ketanserin (0.01-10 mg/kg) and  
      sulpiride (32-320 mg/kg) dose-dependently attenuated  
      the psychological stress lesion formation, and the  
35     activity was arranged in the order of their in vitro  
      binding affinities for the 5-HT<sub>3</sub>, but not 5-HT<sub>1A</sub> or  
      5-HT<sub>2</sub> receptors. In contrast, a peripherally acting

5-HT3 antagonist, M-840 ([3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazol-5-yl]-methyl]trimethyl-ammonium iodide), dopamine acting compounds, haloperidol and FR64822 [N-(4-pyridylcarbamoyl)amino-1,2,3,6-tetrahydropyridine), and antisecretory drugs, atropine and famotidine, minimally affected the lesion formation.

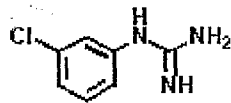
- SDZ ICT 322, an indole-3-carboxylic acid scopine ester

- MD-354

MD-354. We were intrigued by the novel 5-HT3 agonist phenylbiguanide. It seemed quite selective for 5-HT3 receptors, but displayed rather low affinity ( $K_i > 1,000$  nM). In a prior study with Dr. S. Peroutka, we had investigated the SAFIR of various arylpiperazines at 5-HT3 receptors. Arylpiperazines, as mentioned earlier, are relatively nonselective agents; however, many bind at 5-HT3 receptors with significantly higher affinity than phenylbiguanide. We identified some structural similarities between the arylpiperazines and phenylbiguanide and, in collaboration with Milt Teitler, made a series of hybrid analogs that we hoped would bind with higher affinity than phenylbiguanide. Two such analogs were *meta*-chlorophenylbiguanide (mCPBG) and 2-naphthylbiguanide ( $K_i = 10-20$  nM); both displayed significantly higher affinity than phenylbiguanide. Although we reported these compounds in abstract form, a full paper <http://www.phc.vcu.edu/rag/serotonin/-seven> on mCPBG independently appeared by another group of investigators at the same time. It was not until a few years later that we finally published a full paper on these agents. However, in the course of our studies, we identified a novel class of 5-HT3 agonists: the arylguanides. MD-354, for example, was



found to bind at 5-HT<sub>3</sub> receptors with high affinity (K<sub>i</sub> ca. 35 nM) and to display agonist actions in several assay systems.



MD-354

- S 21007 (21007 [5-(4-benzyl piperazin-1-yl)4H pyrrolo [1,2-a]thieno[3,2-e]pyrazine]).

Interaction of S 21007 with 5-HT<sub>3</sub> receptors. In vitro and in vivo characterization.

Delagrangé P, Emerit MB, Merah N, Abraham C, Morain P, Rault S, Renard P, Pfeiffer B, Guardiola-Lemaître B, Hamon M; *Eur J Pharmacol* 1996 Dec 5, 316:2-3:195-203

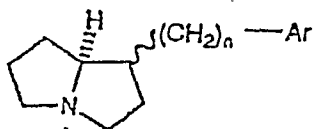
The interaction of S 21007 [5-(4-benzyl piperazin-1-yl)4H pyrrolo [1,2-a]thieno[3,2-e]pyrazine] with serotonin 5-HT<sub>3</sub> receptors was investigated using biochemical, electrophysiological and functional assays. Binding studies using membranes from N1E-115 neuroblastoma cells showed that S 21007 is a selective high affinity (IC<sub>50</sub> = 2.8 nM) 5-HT<sub>3</sub> receptor ligand. As expected of an agonist, S 21007 stimulated the uptake of [14C]guanidinium (EC<sub>50</sub> approximately 10 nM) in NG 108-15 cells exposed to substance P, and this effect could be prevented by the potent 5-HT<sub>3</sub> receptor antagonist ondansetron. In addition, like 5-HT and other 5-HT<sub>3</sub> receptor agonists (phenylbiguanide and 3-chloro-phenylbiguanide), S 21007 (EC<sub>50</sub> = 27 micromM) produced a rapid inward current in N1E-115 cells.

The 5-HT<sub>3</sub> receptor agonist action of S 21007 was also demonstrated in urethane-anaesthetized rats as this drug (120 micrograms/kg i.v.) triggered the Bezold-Jarisch reflex (rapid fall in heart rate), and this action could be prevented by pretreatment with the potent 5-HT<sub>3</sub> receptor antagonist zacopride. Finally, in line with its 5-HT<sub>3</sub> receptor agonist properties, S 21007 also triggered emesis in the ferret. Evidence for 5-HT<sub>3</sub> receptor antagonist-like properties of S 21007 was also obtained in some of these experiments since previous exposure to this compound prevented both the 5-HT-induced current in N1E-115 cells and the Bezold-Jarisch reflex elicited by an i.v. bolus of 5-HT (30 micrograms/kg) in urethane-anaesthetized rats. These data suggest that S 21007 is a selective 5-HT<sub>3</sub> receptor agonist which can exhibit antagonist-like properties either by triggering a long lasting receptor desensitization or by a partial agonist activity at 5-HT<sub>3</sub> receptors in some tissues.

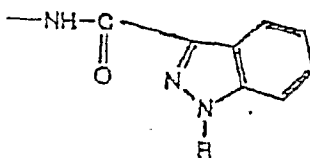
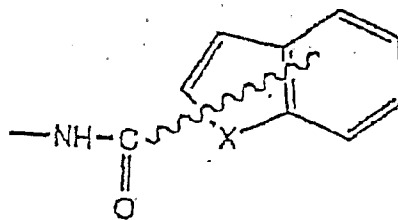
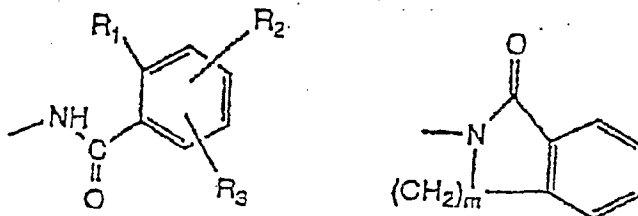
Further, in the following patent publications more compounds useful according to the present invention are presented.

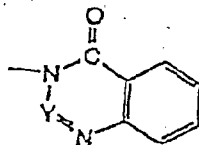
*N*-substituted benzamides

- EP0417746 (September 1990, G.D. Searle & Co) N-Aza-bicyclo/3.3.0/octane amides of aromatic acids. See also US5126343.



or a pharmaceutically acceptable salt thereof  
 wherein  $n$  is 0 or 1;  
 Ar can be





$R^1$  is alkoxy of 1 to 6 carbon atoms; and  
 $R^2$  and  $R^3$  are the same or different and are  
 hydrogen, halogen,  $CF_3$ , hydroxy,  $C_{1-6}$  alkoxy,  $C_{2-7}$   
 acryl, amino, amino substituted by one or two  $C_{1-6}$   
 alkyl groups,  $C_{2-7}$  acylamino, aminocarbonyl or  
 aminosulfone, optionally substituted by one or two  
 $C_{1-6}$  alkyl groups,  $C_{1-6}$  alkyl sulfone or nitro  
 groups; wherein X can be NR, S, or O;  
 Y can be CH or N;  
 R is H, alkyl or aryl; and  
 m is 1 or 2.

The structure is a benzamide with  $Ar=Ph-CONH-$ .

A compound of the formula or a pharmaceutically  
 acceptable salt thereof wherein n is = or 1; and Ar  
 is an aromatic amide moiety, which compound exhibits  
 prokinetic activity and is a 5-HT<sub>3</sub> antagonist.

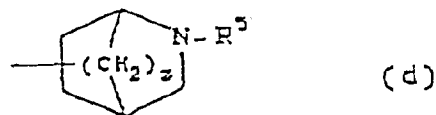
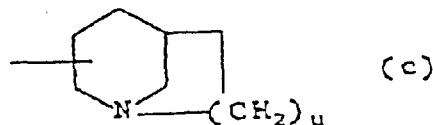
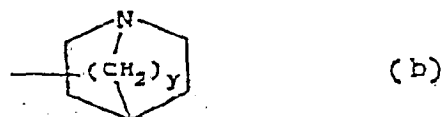
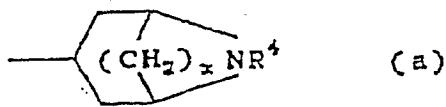
- EP0430190 (November 1990, Syntex, Inc) New tricyclic  
 compounds in which  
 the dashed line denotes an optional double bond;  
 n is 1, 2 or 3;  
 p is 0, 1, 2 or 3;

q is 0, 1 or 2;

each  $R^1$  is independently selected from halogen, hydroxy, lower  $C_{1-6}$  alkoxy (optionally substituted with phenyl), lower  $C_{1-6}$  alkyl, nitro, amino, amino-carbonyl, (lower  $C_{1-6}$  alkyl)amino, di(lower  $C_{1-6}$  alkyl)amino, and (lower  $C_{1-6}$  alkanoyl)amino;

each  $R^2$  is lower  $C_{1-6}$  alkyl; and

$R^3$  is selected from



in which

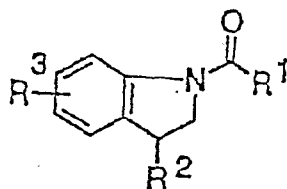
u, x, y and z are all independently an integer from 1 to 3; and

$R^4$  and  $R^5$  are independently  $C_{1-7}$  alkyl,  $C_{3-8}$  cycloalkyl,  $C_{3-8}$  cycloalkyl- $C_{1-2}$  alkyl, or a group

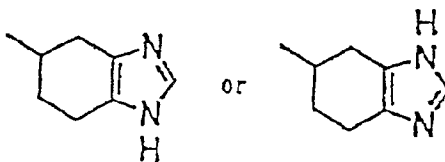
(CH<sub>2</sub>)<sub>t</sub>R<sub>6</sub> where t is 1 or 2 and R<sub>6</sub> is thienyl, pyrrolyl or furyl optionally further substituted by one or two substituents selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by one or two substituents selected from C<sub>1-4</sub> alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and C<sub>1-4</sub> alkyl (optionally substituted by hydroxy, C<sub>1-4</sub> alkoxy, carboxy, esterified carboxy or in vivo hydrolyzable acyloxy); or a pharmaceutically acceptable salt thereof or an N-oxide thereof; or an individual isomer or mixture of isomers thereof. The present invention is directed to new pharmaceutically active compounds with 5-HT<sub>3</sub> receptor antagonist activity of Formula I: in which the dashed line denoted an optional double bond; n is 1, 2 or 3; p is 0, 1, 2 or 3; q is 0, 1 or 2; each R<sub>1</sub> is halogen, hydroxy, alkoxy (optionally substituted with phenyl), alkyl, nitro, amino, amino carbonyl, (alkyl)amino, di(alkyl)amino, and (alkanoyl)amino; each R<sup>2</sup> is alkyl; and R<sub>3</sub> is in which u, x, y and z are all independently an integer from 1 to 3; and R<sub>4</sub> and R<sub>5</sub> are independently alkyl, cycloalkyl, cycloalkylalkyl, or a group (CH<sub>2</sub>)<sub>t</sub>R<sub>6</sub> where t is 1 or 2 and R<sub>6</sub> is thienyl, pyrrolyl or furyl optionally further substituted by one or two substituents selected from alkyl, alkoxy, trifluoromethyl or halogen, or is phenyl optionally substituted by alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy, and alkyl (optionally substituted).

*Indoles, Indole-1-carboxamides and Imidazole derivatives*

- EP0721949 (September 1993, Tokyo Tanabe Coompany Limited) Indoline compound and 5-HT3 receptor antagonist containing the same as active ingredient.



wherein R<sup>1</sup> represents the group

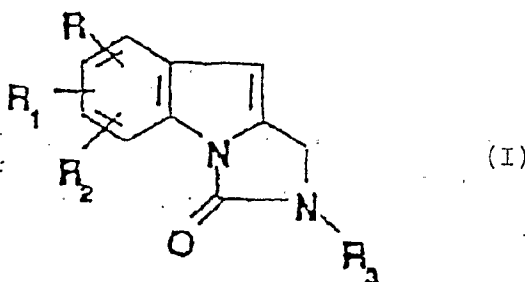


R<sup>2</sup> represents a phenyl group which may be substituted or an aromatic heterocyclic group, and R<sup>3</sup> represents hydrogen, a halogen, or a lower alkyl group, hydroxyl group, lower alkoxy group, carbamoyl group or lower alkoxy carbonyl group, or a physiologically acceptable salt thereof, or its solvate.

An indoline compound represented by general formula (I); a physiologically acceptable salt thereof; solvates of these compounds; and a 5-HT<sub>3</sub> receptor antagonist containing the same as the active ingredient. In formula (I) R<sub>1</sub> represents the group (a) or (b),

R2 represents optionally substituted phenyl or heteroaryl; and R3 represents hydrogen, halogen, lower alkyl, hydroxy, lower alkoxy, carbamoyl or lower alkoxycarbonyl. The compound has a potent antagonism against 5-HT<sub>3</sub> receptors in the intestinal tract as compared with the known 5-HT<sub>3</sub> receptor antagonists and is excellent in the persistence of the activity. Hence it is useful for preventing or treating vomiting or nausea induced by chemotherapy or radiation, irritable bowel syndrome and diarrhea.

- EP0711299 (May 1994, Pharmacia S.p.A) Azabicycloalkyl Derivatives Of Imidazol(1,5-A)Indol-3-One As 5HT<sub>3</sub> Antagonists



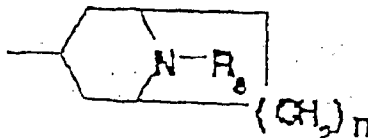
wherein

each of R, R<sub>1</sub> and R<sub>2</sub>, which may be the same or different, is hydrogen, halogen, hydroxy, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylthio, formyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, carboxy, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, nitro, -N(R<sub>4</sub> R<sub>5</sub>) in which each of R<sub>4</sub> and R<sub>5</sub> independently is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, formyl or C<sub>2</sub>-C<sub>6</sub> alkanoyl; or a (R<sub>6</sub> R<sub>7</sub>)N-SO<sub>2</sub> group, in which each of R<sub>4</sub> and R<sub>7</sub> independently is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl; R<sub>3</sub> is a group a)





or b)



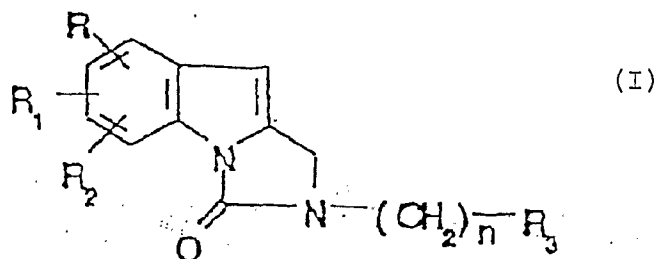
wherein

n is an integer of 1 or 2 and R<sub>8</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by phenyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, formyl or C<sub>2</sub>-C<sub>6</sub> alkanoyl; and the pharmaceutically acceptable salts thereof.

Novel 5-HT<sub>3</sub> receptor antagonist compounds having general formula (I) wherein each of R, R<sub>1</sub> and R<sub>2</sub>, which may be the same or different, is hydrogen, halogen, hydroxy, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylthio, formyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, carboxy, C<sub>1</sub>-C<sub>6</sub> alkyl-carbonyl, nitro, -N(R<sub>4</sub> R<sub>5</sub>) in which each of R<sub>4</sub> and R<sub>5</sub> independently is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, formyl or C<sub>2</sub>-C<sub>6</sub> alkanoyl; or a (R<sub>6</sub> R<sub>7</sub>)N-SO<sub>2</sub> group, in which each of R<sub>6</sub> and R<sub>7</sub> independently is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl; R<sub>3</sub> is a group (a) or (b) wherein n is an integer of 1 or 2 and R<sub>8</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl unsubstituted or substituted by phenyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, formyl or C<sub>2</sub>-C<sub>6</sub> alkanoyl; and the pharmaceutically acceptable salts thereof, are provided.

- EP0711293 (May 1994, Pharmacia S.p.A) Imidaxolylalkyl Derivatives Of Imidazol(1,5-A)Indol-3-One And Their Use As Therapeutic Agents.

65



wherein

n, 1, 2 or 3 is;

each of R, R<sub>1</sub> and R<sub>2</sub>, which may be the same or

different, is hydrogen, halogen, hydroxy, cyano C<sub>1</sub>-

C<sub>6</sub> alkyl, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylthio,

formyl, C<sub>2</sub>-C<sub>6</sub> alkanoyl, carboxy, C<sub>1</sub>-C<sub>6</sub>

alkoxycarbonyl, nitro, -N(R<sub>4</sub>)R<sub>5</sub> in which each of R<sub>4</sub>

and R<sub>5</sub> independently is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl,

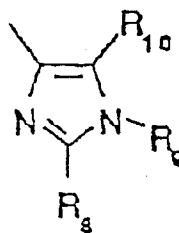
formyl or C<sub>2</sub>-C<sub>6</sub> alkanoyl; or a R<sub>6</sub>(R<sub>7</sub>)N-SO<sub>2</sub> group, in

which each of R<sub>6</sub> and R<sub>7</sub> independently is hydrogen or

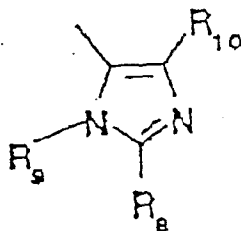
C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sub>3</sub> is an imidazolyl group having the formula

a)



or b)



wherein each of R<sub>6</sub> and R<sub>10</sub>, which may be the same or

different, is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl, R<sub>9</sub> is hydro-

gen, C<sub>1</sub>-C<sub>6</sub> alkyl or a nitrogen protection group

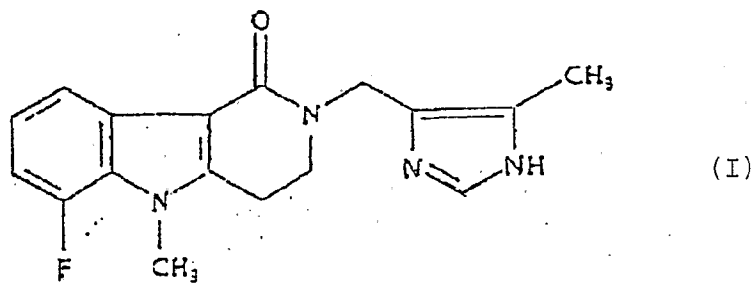
chosen from triphenylmethyl, t-butyloxycarbonyl,

benzyloxycarbonyl, acetyl, formyl, di(p-methoxyphenyl)methyl and (p-methoxyphenyl)diphenylmethyl; and the pharmaceutically acceptable salts thereof.

5 Novel 5-HT<sub>3</sub> receptor antagonist compounds having formula (I), wherein n is 1, 2 or 3; each of R, R<sub>1</sub> and R<sub>2</sub>, which may be the same or different, is hydrogen, halogen, hydroxy, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkylthio, formyl, C<sub>2</sub>-C<sub>6</sub>  
 10 alkanoyl, carboxy, C<sub>1</sub>-C<sub>6</sub> alkoxy-carbonyl, nitro, -N(R<sub>4</sub> R<sub>5</sub>), in which each of R<sub>4</sub> and R<sub>5</sub> independently is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, formyl or C<sub>2</sub>-C<sub>6</sub> alkanoyl; or a (R<sub>6</sub> R<sub>7</sub>)N-SO<sub>2</sub> group, in which each of R<sub>6</sub> and R<sub>7</sub> independently is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl; R<sub>3</sub> is an  
 15 imidazolyl group of formula (a) or (b), wherein each of R<sub>8</sub> and R<sub>10</sub> which may be the same or different is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl, R<sub>9</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or a nitrogen protecting group; and the pharmaceutically acceptable salts thereof, are  
 20 disclosed.

- EP0581388 (July 1993, Glaxo Group Ltd) Pyridoindolone Methansulphonate as 5HT and 5HT<sub>3</sub> receptor antagonists.

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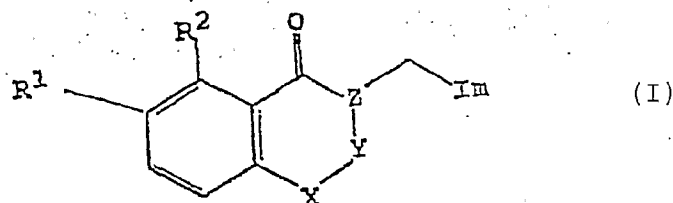


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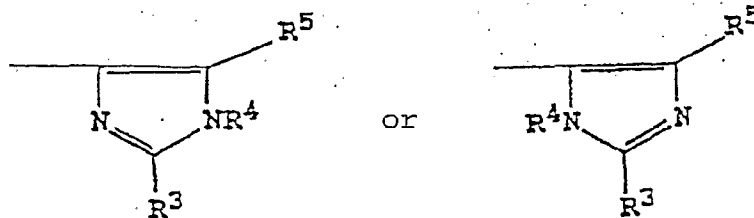
This invention relates to the novel salt 6-fluoro-2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one methane sulphonate, to solvates of this salt, to pharmaceutical compositions containing it and to its use in medicine as 5-HT<sub>3</sub> receptor antagonists.

- EP0364274 (October 1989, Glaxo Group Ltd) Imidazole derivatives.



10

wherein Im represents an imidazolyl group of the formula:



25

and one of the groups represented by R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is a hydrogen atom, or a C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-6</sub> alkenyl, phenyl or phenyl C<sub>1-3</sub> alkyl group, and each of the other two groups, which

30

may be the same or different, represents a hydrogen atom or a C<sub>1-6</sub> alkyl group;

R<sup>1</sup> and R<sup>2</sup> each represent a hydrogen atom, or together with the carbon atoms to which they are attached

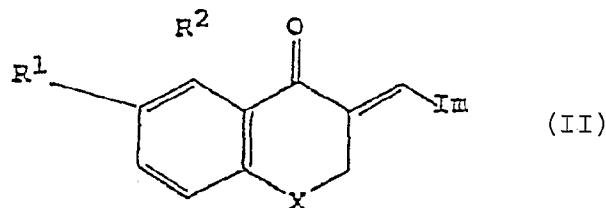
35

form a phenyl ring;

X represents an oxygen or a sulphur atom, or a group NR<sup>6</sup>, wherein R<sup>6</sup> represents a C<sub>1-6</sub> alkyl group;

Z-Y represents the group CH-CH<sub>2</sub> or C=CH;  
and physiologically acceptable salts and solvates  
thereof, which comprises:

(A) for the production of a compound of formula (I)  
in which Z-Y represents the group CH-CH<sub>2</sub>,  
hydrogenating a compound of formula (II):



or a protected derivative thereof, followed if  
necessary by removal of any protecting groups  
present; or

(B) for the production of a compound of formula (I)  
in which Z-Y represents the group C=CH, reacting a  
compound of formula (II), or a protected derivative  
thereof, with an organic acid or a mineral acid,  
followed if necessary by removal of any protecting  
groups present; or

(C) converting a compound of general formula (I)  
into another compound of formula (I) using  
conventional techniques; or

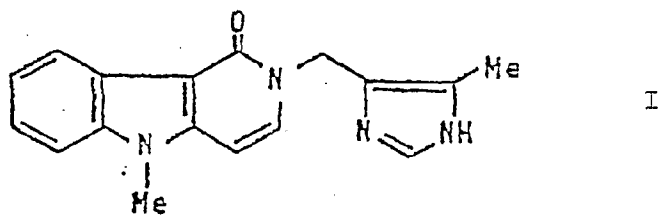
(D) removing protecting group(s) from a protected  
form of a compound of formula (I);  
and when the compound of formula (I) is obtained as  
a mixture of enantiomers, optionally resolving the  
mixture to obtain the desired enantiomer;  
and/or where the compound of formula (I) is in the  
form of a free base, optionally converting the free  
base into a salt.

The invention provides imidazole derivatives of the  
general formula (I) wherein Im represents an imi-  
dazolyl group of the formula: and one of the groups  
represented by R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> is a hydrogen atom, or

a C1-C6 alkyl, C3-7 cycloalkyl, C3-6 alkenyl, phenyl or phenyl C1-3 alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C1-6 alkyl group; R1 and R2 each represent a hydrogen atom, or together with the carbon atoms to which they are attached form a phenyl ring; X represents an oxygen or a sulphur atom, or a group NR6, wherein R6 represents a C1-6 alkyl group; Z-Y represents the group CH-CH2 or C=CH; and physiologically acceptable salts and solvates thereof. The compounds of formula (I) are potent and selective antagonists of 5-hydroxytryptamine at 5-HT3 receptors and are useful, for example, in the treatment of psychotic disorders, anxiety and nausea and vomiting.

- EP0392663 (March 1989, One Pharmaceutical Co. Ltd)  
Carboline derivative as a 5-HT3 receptor antagonist.

A  $\gamma$ -carboline of the formula I



or pharmaceutically acceptable acid addition salt and/or hydrate thereof for use in a method of treatment or prophylaxis of diseases or conditions induced by the action of 5-hydroxytryptamine on 5-hydroxytryptamine 3-receptors in a mammal, including man.

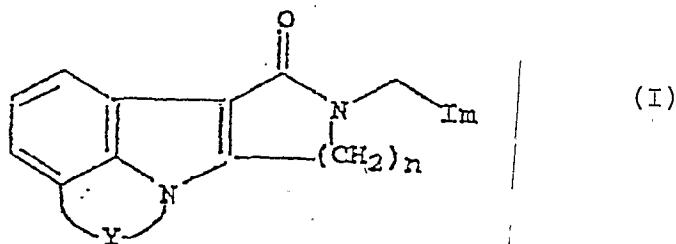
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The present invention provides  $\gamma$ -carboline of the formula: or non-toxic acid additional salts thereof

and/or hydrates thereof, for use as 5-HT<sub>3</sub> receptor antagonists. The present invention also provides pharmaceutical compositions comprising compounds of the formula I.

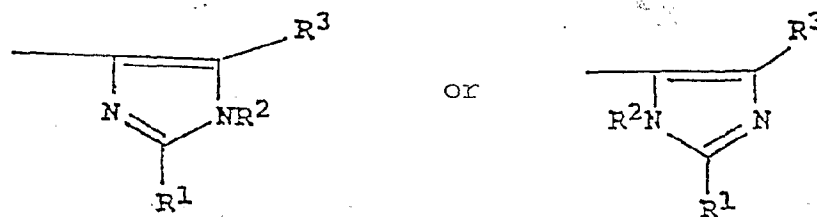
- EP0357417 (August 1989, Glaxo Group Ltd) Lactam derivatives.

Compounds of the general formula (I)



wherein n represents 2 or 3;

Im represents an imidazolyl group of the formula:



wherein one of the groups represented by R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> is a hydrogen atom or a C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-6</sub> alkenyl, phenyl or phenyl C<sub>1-3</sub> alkyl- group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C<sub>1-6</sub> alkyl group;

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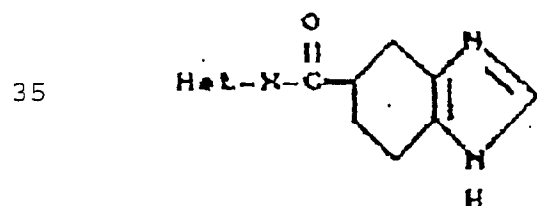
Y represents a group  $-(CH_2)_m-$ , wherein m represents 2, 3 or 4; or Y represents a group  $-X(CH_2)_p-$ , C1-6 alkyl group, and X is attached to the benzene ring moiety of the molecule;

5 and physiologically acceptable salts and solvates thereof.

The invention provides lactam derivatives of the general formula (I) wherein n represents 2 or 3; Im represents an imidazolyl group of the formula:  
 10 wherein one of the groups represented by R1, R<sup>2</sup> and R3 is a hydrogen atom or a C1-6 alkyl, C3-7 cycloalkyl, C3-6 alkenyl, phenyl or phenyl C1-3 alkyl-group, and each of the other two groups, which  
 15 may be the same or different, represents a hydrogen atom or a C1-6 alkyl group; Y represents a group  $-(CH_2)_m-$ , wherein m represents 2, 3 or 4; or Y represents a group  $-X(CH_2)_p-$ , wherein p represents 2 or 3, X represents an oxygen or a sulphur atom or a  
 20 group NR4, where R4 is a C1-6 alkyl group, and X is attached to the benzene ring moiety of the molecule; and physiologically acceptable salts and solvates thereof. The compounds of formula (I) are potent and selective antagonists of 5-hydroxytryptamine at 5-HT3 receptors and are useful, for example in the  
 25 treatment of psychotic disorders, anxiety and nausea and vomiting.

• RU2059623 Tetrahydrobenzimidazole derivatives or its  
 30 pharmaceutically acceptable salt.

tetrahydrobenzimidazole derivative of the formula

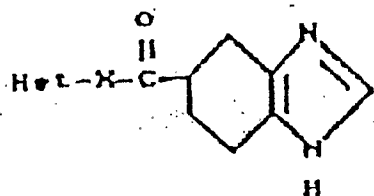


and a pharmaceutical



72

composition containing an effective amount of compound



and a pharmaceutically

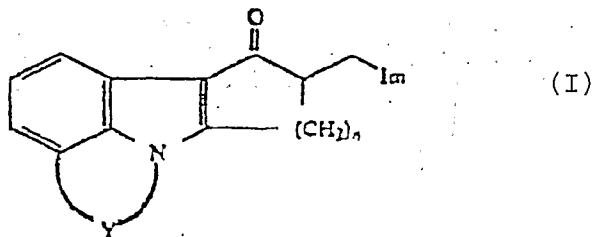
acceptable carrier showing activity of a 5-HT<sub>3</sub> receptor antagonist.

10

- US5,045,545 (May 1989, Glaxo Group Limited) [(Imidazol-4(and 5)-yl)methyl] tetracyclic ketones having 5-HT<sub>3</sub> antagonist activity.

15

The invention relates to tetracyclic ketones of the general formula (I)

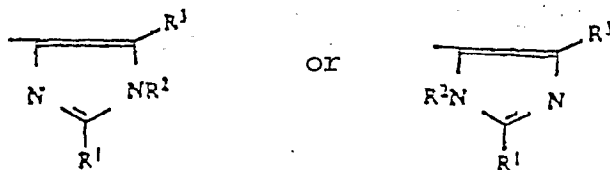


wherein

n represents 1, 2 or 3;

25

Im represents an imidazolyl group of the formula:



35

wherein one of the groups represented by  $R^1$ ,  $R^2$  and  $R^3$  is a hydrogen atom or a  $C_{1-6}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{3-6}$  alkenyl, phenyl or phenyl  $C_{1-3}$  alkyl group, and each of the other two groups, which  
5 may be the same or different, represents a hydrogen atom or a  $C_{1-6}$  alkyl group;  
Y represents a group  $-(CH_2)_m-$ , wherein m represents 2, 3 or 4; or a group  $-X(CH_2)_p-$ , where p represents 2 or 3, X represents an oxygen or a sulphur atom or  
10 a group  $NR^4$ , where  $R^4$  is a  $C_{1-6}$  alkyl group, and X is attached to the benzene ring moiety of the molecule;  
and physiologically acceptable salts and solvates thereof.

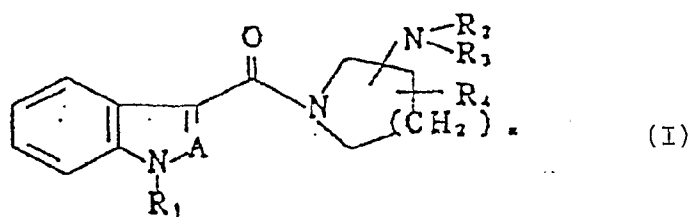
15 The compounds are potent and selective antagonists of the effect of 5-HT<sub>3</sub> receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.

20 The invention relates to tetracyclic ketones of the general formula (I)##STR1## wherein n represents 1, 2 or 3; Im represents an imidazolyl group of the formula: ##STR2## wherein one of the groups represented by  $R_{sup.1}$ ,  $R_{sup.2}$  and  $R_{sup.3}$  is a hydrogen  
25 atom or a  $C_{sub.1-6}$  alkyl,  $C_{sub.3-7}$  cycloalkyl,  $C_{sub.3-6}$  alkenyl, phenyl or phenyl  $C_{sub.1-3}$  alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom  
30 or a  $C_{sub.1-6}$  alkyl group; Y represents a group  $-(CH_{sub.2})_m-$ , where m represents 2, 3 or 4, or a group  $-X(CH_{sub.2})_{sub.p}-$ , where p represents 2 or 3, X represents an oxygen or a sulphur atom or a group  $NR_{sup.4}$ , where  $R_{sup.4}$  is a  $C_{sub.1-6}$  alkyl  
35 group, and X is attached to the benzene ring moiety of the molecule; and physiologically acceptable salts and solvates thereof. The compounds are potent

and selective antagonists of the effect of 5-HT at 5-HT<sub>3</sub> receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.

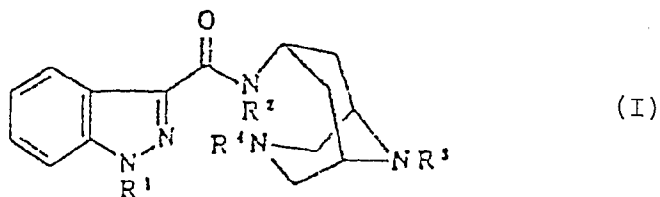
#### Indazole carboxamide derivatives

- EP0630893 (March 1992, Kyorin Pharmaceutical Co., Ltd.) N,N'-Disubstituted Amide Derivative.



A 5-HT<sub>3</sub> antagonist containing a novel N,N'-disubstituted amide derivative having a potent and selective 5-HT<sub>3</sub> receptor antagonism, represented by general formula (I), a hydrate thereof, or an acid addition salt thereof, wherein R<sub>1</sub> represents hydrogen or lower alkyl; R<sub>2</sub> and R<sub>3</sub> may be the same or different from each other and each represents hydrogen, lower alkyl, lower alkenyl, aryl-substituted lower alkyl which may be substituted, acyl or lower alkoxy carbonyl; R<sub>4</sub> represents hydrogen, lower alkyl or lower alkoxy; A represents CH or N; and n represents 1, 2 or 3.

- EP0558923 (January 1992, Nisshin Flour Milling Co., Ltd.) Diazabicyclo derivatives as 5-HT<sub>3</sub> antagonists



wherein

R<sup>1</sup> is alkyl, 3-methyl-2-butenyl, cyclopropylmethyl, 2-propynyl, cyanomethyl, 2-oxopropyl, 2-hydroxypropyl, 2-pyridylmethyl, methoxycarbonylmethyl, 2-ethoxyethyl, isobutoxycarbonyl, or 4,6-diamino-2-triazinylmethyl;

R<sup>2</sup> is hydrogen; and

R<sup>3</sup> and R<sup>4</sup> are methyl.

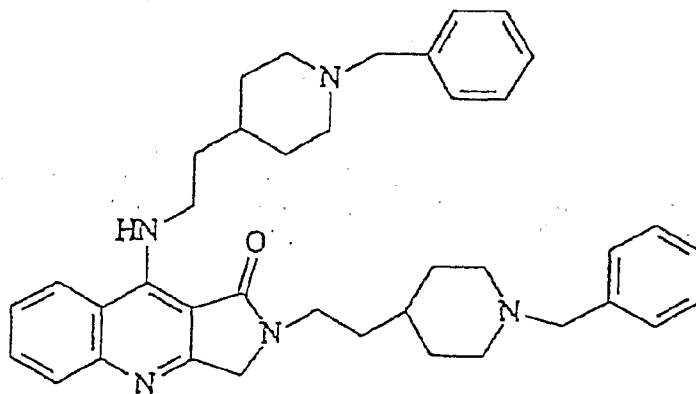
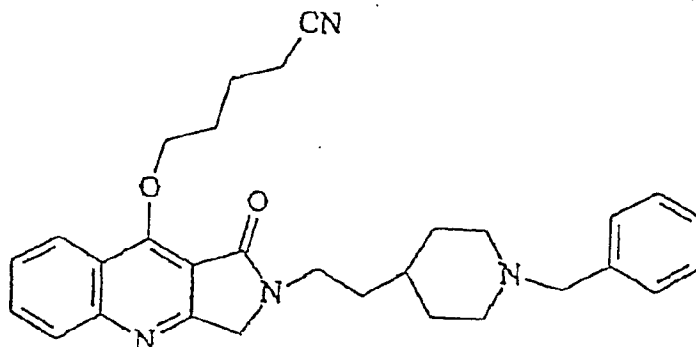
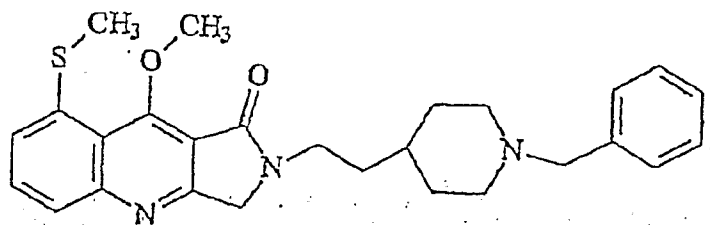
Diazabicyclo derivatives of formula (I) and pharmaceutically acceptable salts thereof: wherein R<sup>1</sup> is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, oxoalkyl, alkoxy-carbonylalkyl, alkoxycarbonyl, acyl, dialkylamino-alkyl, hydroxyalkyl, haloalkyl, cyanoalkyl, hetero-cycloalkyl, aryl, heteroarylalkyl or arylalkyl, the aryl group and the aryl moiety being optionally substituted by alkoxy, nitro, alkyl, amino or halo; R<sup>2</sup> is hydrogen or alkyl; R<sup>3</sup> and R<sup>4</sup> may be the same or different and each is hydrogen, alkyl, alkenyl, acyl, alkoxyalkyl or arylalkyl wherein the aryl moiety is optionally substituted by alkoxy, nitro, alkyl, amino or halo; with the proviso that when R<sup>2</sup> is hydrogen and both R<sup>3</sup> and R<sup>4</sup> are methyl, R<sup>1</sup> does not represent hydrogen, alkyl, unsubstituted benzyl or dimethylaminoethyl; having 5-HT<sub>3</sub> receptor antagonist activity.

### *Quinolines and Isoquinolines*

- WO9964421 (June 1999, Arena Pharmaceuticals, Inc) Acetylcholine enhancers.

An acetylcholine enhancer selected from the group consisting of the chemical compounds represented by the following structures:

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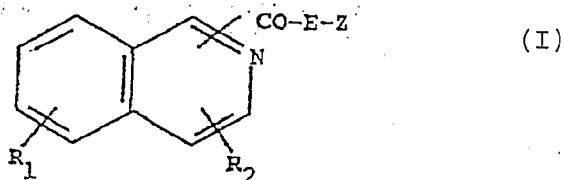


Disclosed herein are quinoline derivatives having  
dual mechanistic properties, referred to in this  
patent documents as "acetylcholine enhancers", i.e.,  
compounds which evidence acetylcholinesterase (AChE)  
inhibition activity, and 5-HT<sub>3</sub> receptor antagonist  
activity. A particularly preferred compound is 2-[2-  
(1-benzylpiperizin-4-yl)ethyl]-2,3-dihydro-9-methoxy-  
1H-pyrrolo[3,4-b]quinolin-1-one hemifumarate, refer-  
red to herein as Compound A ("Cm.A").

- EP0526545 (April 1991, Beecham Group p.l.c.)  
Isoquinoline Amides And Esters As 5-HT<sub>3</sub> Receptor  
Antagonists.

77

A compound of formula (I), or a pharmaceutically acceptable salt thereof:



10 wherein

E is NH or O,

R<sub>1</sub> is hydrogen, halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, hydroxy or nitro;

15 Z is an azacyclic or azabicyclic side chain; and

i) the group CO-E-Z is in the 1-position and either R<sub>2</sub> is in the 3-position and is hydrogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy, or R<sub>2</sub> is in the 4-position and is hydrogen, halogen, CF<sub>3</sub>, C<sub>1-6</sub> alkyl, C<sub>1-7</sub> acyl, C<sub>1-7</sub> acylamino, phenyl optionally substituted by one or two C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy or halogen groups, or amino, aminocarbonyl or aminosulphonyl, optionally substituted by one or two C<sub>1-6</sub> alkyl or C<sub>3-8</sub> cycloalkyl groups or by C<sub>4-5</sub> polymethylene or by phenyl, C<sub>1-6</sub> alkylsulphonyl, C<sub>1-6</sub> alkylsulphanyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, hydroxy or nitro; or

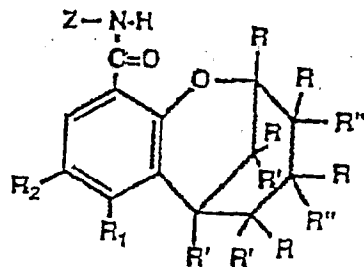
30 ii) the group CO-E-Z is in the 3-position and either R<sub>2</sub> is in the 1-position and is hydrogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy, or R<sub>2</sub> is in the 4-position and is hydrogen or C<sub>1-6</sub> alkoxy;

35 having 5-HT<sub>3</sub> receptor antagonist activity.

Isoquinoline derivatives (I) having 5-HT<sub>3</sub> receptor antagonist activity, a process for their preparation and their use as pharmaceuticals. In formula (I) E is NH or O, R<sub>1</sub> is hydrogen, halogen, alkyl, alkoxy, hydroxy or nitro; Z is an azacyclic or azabicyclic side chain, such as a group of formula (a), (b) or (c) wherein; p is 1 or 2; q is 1 to 3; r is 1 to 3; R<sub>3</sub> or R<sub>4</sub> is hydrogen or alkyl, and Y is a group -CH<sub>2</sub>-X-CH<sub>2</sub>- wherein X is -CH<sub>2</sub>-, oxygen, sulphur or X is a bond; and (I) when the group CO-E-Z is in the 1-position and either R<sub>2</sub> is in the 3-position and is hydrogen, alkyl, or alkoxy, or R<sub>2</sub> is in the 4-position and is hydrogen CF<sub>3</sub>, alkyl, acyl, acyl-amino (substituted) phenyl or (substituted) amino, (substituted) aminocarbonyl or (substituted) amino-sulphonyl; (II) the group CO-E-Z is in the 3-position and either R<sub>2</sub> is in the 1-position and is hydrogen, alkyl or alkoxy or R<sub>2</sub> is in the 4-position and is hydrogen or alkoxy.

- EP0628043 (February 1992, Merrell Dow Pharmaceutical Inc) 2,6-Methano-2H-Quinolizin As 5-HT<sub>3</sub>-Receptor Antagonist

A compound of the formula:



where

R is hydrogen or alkyl;

$R_1$  is hydrogen, amino, mono- and di-alkylamino, acylamino, halo or haloalkyl;

$R_2$  is hydrogen, halo, sulfamyl, mono- and di-alkylsulfamyl or haloalkyl;

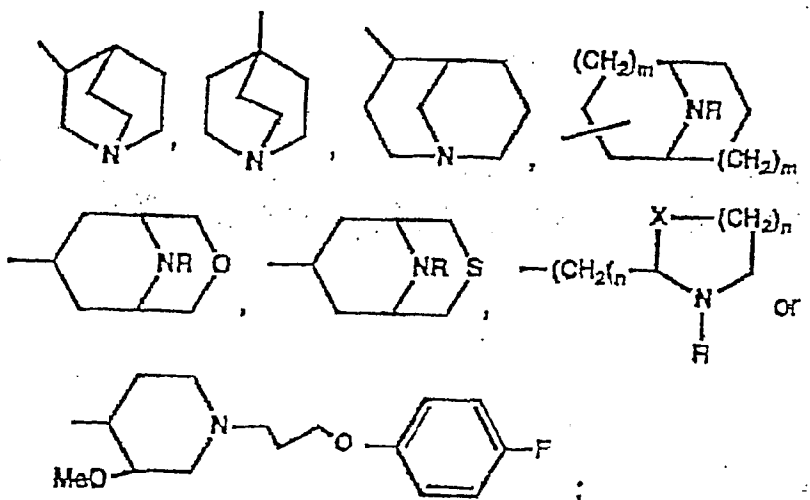
5  $R'$  and  $R''$  are independently hydrogen or alkyl; vicinal  $R'$  and/or  $R''$  groups may form a C=C double bond;

geminal  $R$  and  $R'$  and  $R$  and  $R''$  groups may be  $-(CH_2)_n-$  where  $n$  is 2 to 6;

10

$Z$  is

15



20

25

30

where  $m$  is 0-2,  $n$  is 1-2 and  $X$  is N or S; or pharmaceutically acceptable salts thereof.

35

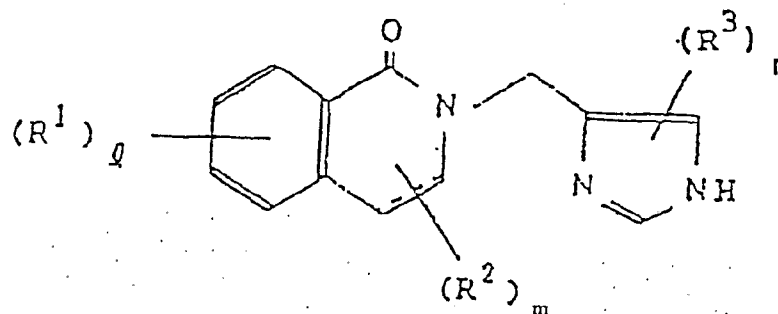
This invention relates to 5-chloro-2,3-dihydro-2,2-dimethylbenzofuran-7-carboxylic acid-octahydro-3-hydroxy-2,6-methano-2H-quinolizin-8-yl ester (I), a novel 5-HT<sub>3</sub>-receptor antagonist, its method of preparation, and to its end-use application in the



treatment of radio- and chemo-therapeutically-  
 induced nausea and vomiting, in the treatment of  
 pain associated with migraine, in the treatment of  
 cognitive disorders, in treating hallucinatory  
 5 endogenous psychoses of the type manifested in  
 patients suffering from schizophrenia and mania, for  
 irritable bowel syndrome, and to combat drug abuse.

• EP0482939 (October 1991, Ono Pharmaceuticals)

10 Isoquinolinone derivative.



wherein each substituent  $R^1$  is the same or different  
 and is hydrogen, halogen,  $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy or  
 25 a group of formula:



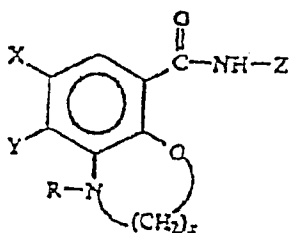
wherein  $R^4$  is hydrogen,  $C_{1-4}$  alkyl or  $C_{2-4}$  alkanoyl  
 30 and  $R^5$  is hydrogen,  $C_{1-4}$  alkyl or benzyl;  
 each substituent  $R^2$  is the same or different and is  
 hydrogen or  $C_{1-4}$  alkyl;  
 each substituent  $R^3$  is the same or different and is  
 hydrogen or  $C_{1-4}$  alkyl;  
 35  $l$  is 1, 2, 3 or 4;  
 $m$  is 1 or 2;  
 $n$  is 1 or 2 and

=== is a single bond or double bond; or a non-toxic acid addition salt thereof or a hydrate thereof.

Isoquinolinone derivatives of the formula: wherein  
 5 R<sup>1</sup> is hydrogen, C1-4 alkyl, C1-4 alkoxy or a group of formula: -NR<sup>4</sup>R<sup>5</sup> wherein R<sup>4</sup> is hydrogen, halogen, C1-4 alkyl or C2-4 alkanoyl and R<sup>5</sup> is hydrogen, C1-4 alkyl or benzyl; R<sup>2</sup> is hydrogen or C1-4 alkyl; R<sup>3</sup> is hydrogen or C1-4 alkyl; l is 1, 2, 3 or 4; m is 1 or  
 10 2; n is 1 or 2 and --- is a single bond or double bond an non-toxic acid addition salts thereof and are useful for the prevention and/or treatment of diseases induced when 5-HT acts on 5-HT<sub>3</sub> receptors (especially vomiting induced by the administration  
 15 of an anti-cancer agent).

*Benzofuranes, Benzooxazines and Benzo(di)azepines*

- US4935511 (September 1989, Rorer Pharmaceutical Corporation) Benzoxazine benzooxazipine carboxamide 5-HT<sub>3</sub> antagonists.



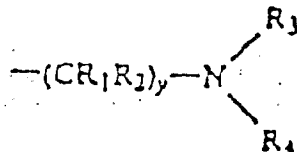
where

X is hydrogen, halo, sulfamyl, alkylsulfamyl or alkylsulfonyl;

Y is hydrogen, amino, mono- or di-alkylamino or halo;

Z is

5



10 3-quinuclidine, 4-quinuclidine, 4-(1-azabicyclo[3.3.1]nonane), 3-(9-methylazabicyclo[3.3.1]nonane) or 4-[3-methoxy-1-(3(-[4-fluorophenoxy]propyl)piperidine)];

15 R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are independently: hydrogen or alkyl;

x is 2 or 3;

y is 1 to 4;

and pharmaceutically acceptable salts thereof.

20 This invention relates to benzoxazine and benzoxazepine carboxamide compounds which exhibit 5-HT<sub>sub.3</sub> antagonist properties including CNS, anti-emetic and gastric prokinetic activity and which are void of any significant D<sub>sub.2</sub> receptor binding  
25 affinity. This invention also relates to pharmaceutical compositions and methods for the treatment of gastrointestinal and mental disorders using said compounds.

30 • IL 107654 Use of substituted N-3,4-dihydro-4-oxo-2,2-pyrimidyl)amino alkyl-4-piperidinyl 2,2-dimethyl-7-benzofuran and benzopyrancarboxamide.

35 A pharmaceutically acceptable acid addition salt form or a stereochemically isomeric form thereof, wherein

R<sub>1</sub> and R<sub>2</sub> represent hydrogen, or

R1 and R2 taken together from a bivalent radical of formula

-CH=CH-CH=CH- (a) -

-CH=C(Cl)-CH=CH- (b) or

5 -CH=CH-C(Cl)=CH- (c);

n represents 2, 3 or 4;

R3 represents hydrogen or methoxy;

m represents 1 or 2;

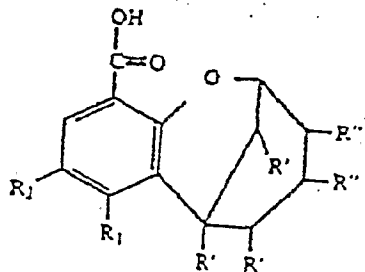
10 R4 represents hydrogen, amino or C1.3alkylcarbonyl-amino; and

R5 represents hydrogen or halo,

for the manufacture of a medicament for treating 5-HT3-mediated disorders.

- 15 • US5288731 (August 1992, Rhone-Poulenc Rorer Pharmaceuticals Inc) 2,6-Methano-2H-1-Benzoxacincarboxylic acids, esters and amides.

20



25

and its stereoisomers, enantiomers, diastereoisomers and racemic mixtures with an amine of the formula

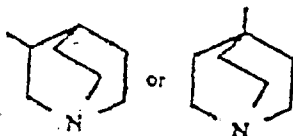
30 H<sub>2</sub>N-Z;

where

R<sub>1</sub> is hydrogen, an amino or alkylamino optionally substituted with a protecting group halo or haloalkyl;

35 R<sub>2</sub> is hydrogen, halo, sulfamyl, mono- and di-alkyl-sulfamyl or haloalkyl;

R' and R'' are hydrogen or alkyl; and Z is:



and its racemic mixtures and stereospecific isomers.

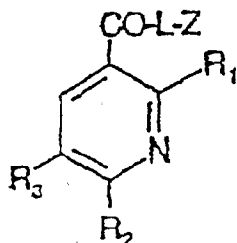
Novel compounds which are 2,6-methano-2H-1-benzoxo-  
cincaboxamides having 5-HT<sub>3</sub>-antagonist  
properties including unique CNS, antiemetic and  
gastric prokinetic activities and which are void of  
any significant D<sub>2</sub> receptor binding affinity,  
therapeutic compositions and methods of treatment of  
disorders which result from 5-HT<sub>3</sub> activity  
using said compounds. Processes for their  
preparation and the preparation of their  
intermediates are also disclosed.

- WO9209284 2,6-Methano-2-H-1-benzoxacincarcboxamides as 5-HT<sub>3</sub> antagonists.

*Other 5-HT<sub>3</sub> antagonist compounds*

- EP0611370 (October 1992, Smithkline Beecham Plc)  
Pyridine-3-Carboxylic Acid Esters Or Amides Useful As  
5-HT<sub>3</sub> Antagonists.

A compound of formula (I), or a pharmaceutically  
acceptable salt thereof:



(I)

wherein

5 R<sub>1</sub> is C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkoxy or C<sub>3-8</sub> cycloalkyl C<sub>1-4</sub> alkoxy;

R<sub>2</sub> is hydrogen, halo, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy or amino optionally substituted by one or two C<sub>1-6</sub> alkyl groups;

R<sub>3</sub> is hydrogen, halo or C<sub>1-6</sub> alkyl;

10 L is O or NH; and

Z is a di-azacyclic or azabicyclic side chain; having 5-HT<sub>3</sub> receptor antagonist activity.

Compounds of formula (I) and pharmaceutically acceptable salts thereof wherein R<sub>1</sub> is C<sub>1-6</sub> alkoxy, C<sub>3-8</sub> cycloalkoxy or C<sub>3-8</sub> cycloalkyl C<sub>1-4</sub> alkoxy; R<sub>2</sub> is hydrogen, halo, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy or amino optionally substituted by one or two C<sub>1-6</sub> alkyl groups; R<sub>3</sub> is hydrogen, halo or C<sub>1-6</sub> alkyl; L is O or NH; and Z is a di-azacyclic or azabicyclic side chain; having 5-HT<sub>3</sub> receptor antagonist activity.

• EP0607233 (October 1991, Smithkline Beecham Plc) 3,9-Diazabicyclo(3.3.1)Nonane Derivatives With 5-HT<sub>3</sub> Receptor Antagonist Activity

A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

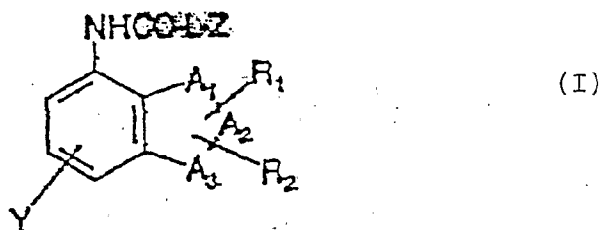
wherein

X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring;  
 A is a linking moiety;  
 Z is a carboxylic acyl group; and  
 R is hydrogen or methyl;  
 having 5-HT<sub>3</sub> receptor antagonist activity.

Compounds of formula (I), and pharmaceutically acceptable salts thereof, wherein X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring; A is a linking moiety; Z is a carboxylic acyl group; and R is hydrogen or methyl; having 5-HT<sub>3</sub> receptor antagonist activity.

- WO9308185 (January 1991, Smithkline Beecham Plc) N-Aryl-N1-Azabicyclo-Ureas As 5-HT<sub>3</sub> Antagonists

A compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein

A<sub>1</sub>, A<sub>2</sub>, A<sub>3</sub> and the carbon atoms to which they are attached form a 5- or 6-membered non-aromatic heterocyclic ring containing at least one -O-, -CO- or -N-;

R<sub>1</sub> and R<sub>2</sub> are hydrogen or C<sub>1-6</sub> alkyl;

Y is hydrogen, halo, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy;

L is O or NH;

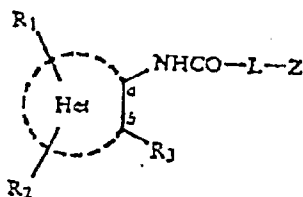
Z is an azabicyclic side chain;

5 having 5-HT<sub>3</sub> receptor antagonist activity.

Compounds of formula (I) and pharmaceutically acceptable salts thereof, wherein A<sub>1</sub>, A<sub>2</sub>, A<sub>3</sub> and the carbon atoms to which they are attached form a  
 10 5- or 6-membered non-aromatic heterocyclic ring containing at least one -O-, -CO- or -N-; R<sub>1</sub> and R<sub>2</sub> are hydrogen or C<sub>1-6</sub> alkyl; Y is hydrogen, halo, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy; L is O or NH; Z is an azabicyclic side chain; having 5-HT<sub>3</sub> receptor  
 15 antagonist activity.

- US4808588 (July 1987, Beecham Group) Heterocyclic ureas and carbonates useful as pharmaceuticals.

20



(I)

25

wherein

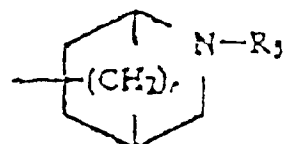
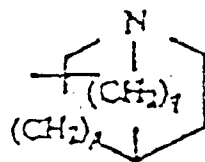
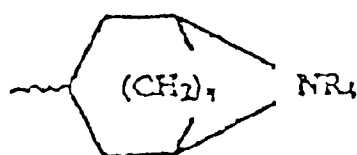
Het is monocyclic heteroaryl having two adjacent  
 30 carbon atoms, a and b, depicted in formula (I) selected from the group consisting of pyridine, pyrimidine, pyrazine, pyrrole, imidazole, thiophene, furan, oxazole and thiazole;  
 R<sub>1</sub> and R<sub>2</sub> are independently selected from hydrogen,  
 35 halogen, CF<sub>3</sub>, C<sub>1-6</sub> alkyl and C<sub>1-6</sub> alkoxy;  
 R<sub>3</sub> is hydroxy, C<sub>1-6</sub> alkoxy, C<sub>3-7</sub> alkenyl-methoxy, phenoxy or phenyl C<sub>1-4</sub> alkoxy in which either phenyl



moiety may be substituted by one or two C<sub>1-6</sub> alkyl,  
 C<sub>1-6</sub> alkoxy or halo; CO<sub>2</sub>R<sub>6</sub> wherein R<sub>6</sub> is hydrogen or  
 C<sub>1-6</sub> alkyl, CONR<sub>7</sub>R<sub>8</sub> or SO<sub>2</sub>NR<sub>7</sub>R<sub>8</sub> wherein R<sub>7</sub> and R<sub>8</sub>  
 are independently hydrogen or C<sub>1-6</sub> alkyl or together  
 are C<sub>4-6</sub> polymethylene, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>m</sub>OR<sub>9</sub> wherein m is  
 1 or 2 and R<sub>9</sub> is C<sub>1-6</sub> alkyl or S(O)<sub>n</sub>R<sub>10</sub> wherein n is  
 0, 1 or 2 and R<sub>10</sub> is C<sub>1-6</sub> alkyl;

L is NH or O;

Z is a group of formula (a), (b) or (c):



wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is  
 1 to 3; and

R<sub>4</sub> or R<sub>5</sub> is C<sub>1-4</sub> alkyl.

Compounds of formula (I), or a pharmaceutically  
 acceptable salt thereof: ##STR1## wherein: Het is  
 monocyclic heteroaryl having two adjacent carbons  
 atoms, a and b, depicted in formula (I); p1 R.sub.1  
 and R.sub.2 are independently selected from

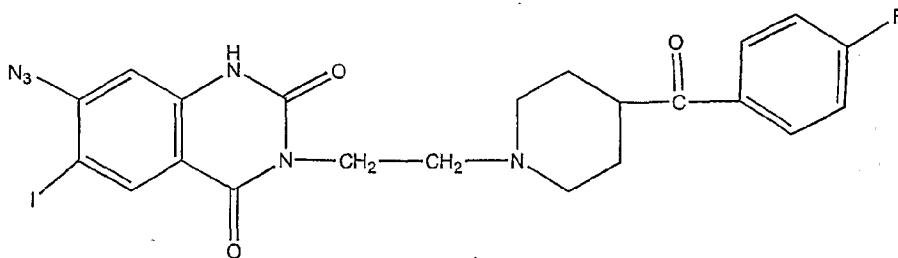
hydrogen, halogen, CF.sub.3, C.sub.1-6 alkyl and C.sub.1-6 Alkoxy; R.sub.3 is hydroxy, C.sub.1-6 alkoxy, C.sub.3-7 alkenyl-methoxy, phenoxy or phenyl C.sub.1-4 alkoxy in which either phenyl moiety may be substituted by one or two C.sub.1-6 alkyl, C.sub.1-6 alkoxy or halo; Co.sub.2 R.sub.6 wherein R.sub.6 is hydrogen or C.sub.1-6 alkyl, CONR.sub.7 R.sub.8 or SO.sub.2 NR.sub.7 R.sub.8 wherein R.sub.7 and R.sub.8 are independently hydrogen or C.sub.1-6 alkyl or together are C.sub.4-6 polymethylene, NO.sub.2, (CH.sub.2).sub.m OR.sub.9 wherein m is 1 or 2 and R.sub.9 is C.sub.1-6 alkyl or S(O).sub.n R.sub.10 wherein n is 0, 1 or 2 and R.sub.10 is C.sub.1-6 alkyl; L is NH or O; Z is a group of formula (a), (b) or (c); ##STR2## wherein n is 2 or 3; p is 1 or 2; q is 1 to 3; r is 1 to 3; and R.sub.4 or R.sub.5 is C.sub.1-4 alkyl; having 5-HT.sub.3 antagonist activity, a process for their preparation and their use as pharmaceuticals.

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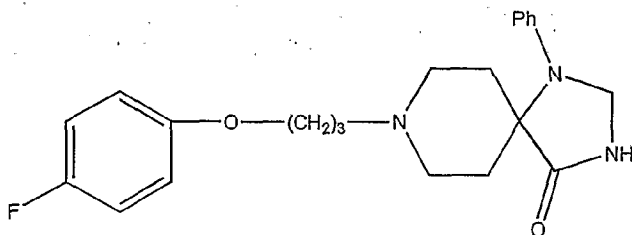
The most preferred 5-HT<sub>3</sub> receptor antagonist is tropanyl-3,5-dimethylbenzoate.

According to the present invention several known substances are, unexpectedly, able to induce airway smooth muscle relaxation by blocking the constricting 5-HT<sub>2</sub> receptor. Such antagonists are selected from the following groups and substances: Ketanserin, i.e. 7-azido-3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-6-iodo-2,4(1H, 3H)-quinazolinedione, having the structural formula:

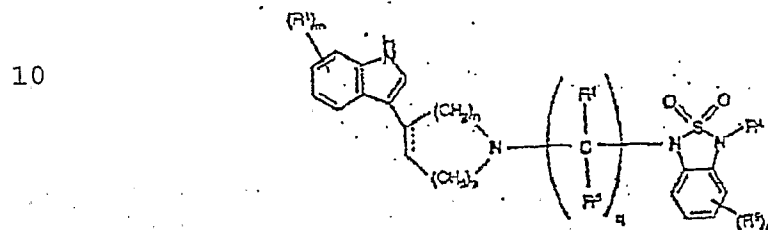
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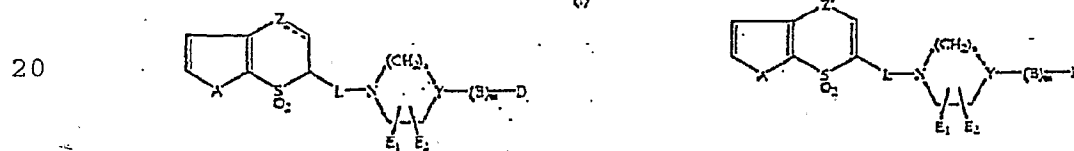
AMI-193, i.e. 8-[3-(4-fluorophenoxy)propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, having the structural formula:



1-((indolyl azacycloalkyl)alkyl)-2,1,3-benzothiadiazole 2,2-dioxides with the following structure (see WO 00/49017).



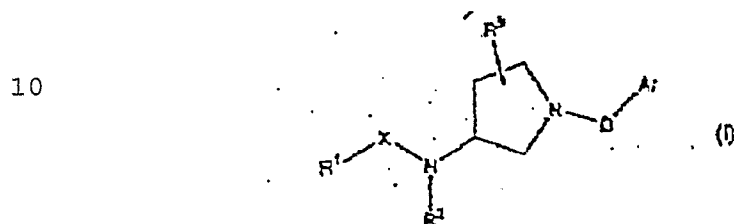
thiopyran derivatives represented by the following formula (I) or (I'), or the salt thereof (see US 6,100,265).



wherein A is S or -CH=CH-; the dotted line indicates that the bond may be either present or absent; Z and Z' are typically



L is an ethylene or trimethylene group; Y is CH or N; n is 2; B is a carbonyl group; m is 0 or 1; D is a phenyl group; and E<sub>1</sub> and E<sub>2</sub> are hydrogen atoms, pyrrolidine compounds with the following structure:  
(see WO 00/26186)



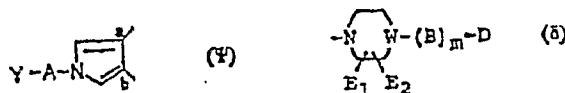
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Pyrrolothiazine and pyrrolothiazepine compounds (see EP 0 970 089)

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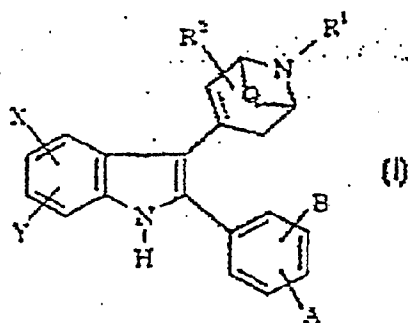
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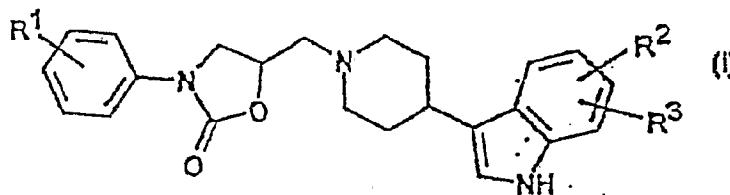
(a pyrrolesulfonamide compound having formula (I) wherein the ring P represented by α is a pyrrole ring having structure β or γ wherein A represents alkylene, alkenylene or alkynylene; and Y represents a group δ in which W represents CH, C= or N; m stands for 0 or 1 when W is CH or N, or m stands for 1 when W is C=; B represents a specific divalent group; E<sub>1</sub> and E<sub>2</sub> each independently represents H or lower alkyl; and D represents an aromatic hydrocarbon group or heterocyclic group; *l* stands for 0 or 1; the dashed line indicates the presence or

absence of a bond; and, when the bond is present,  $Z_2$  is not present and  $Z_1$  represents H but, when the bond is absent,  $Z_1$  represents H and  $Z_2$  represents OH or  $Z_1$  and  $Z_2$  are combined together to represent O or a group  $NOR_5$ , in which  $R_5$  represents H, or alkyl, aralkyl or aryl; and R represents H, alkyl, cycloalkyl, cycloalkyl-alkyl or aralkyl.

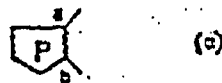
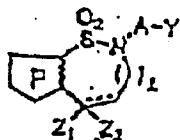
Azabicyclo-substituted phenylindole derivatives with the following formula (see WO 00/04017).

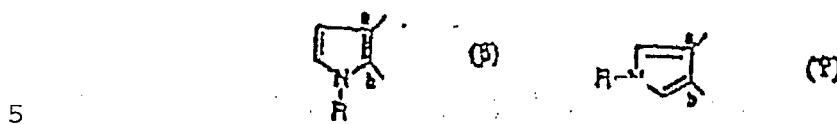


Oxazolidines (see EP 0 964 863)



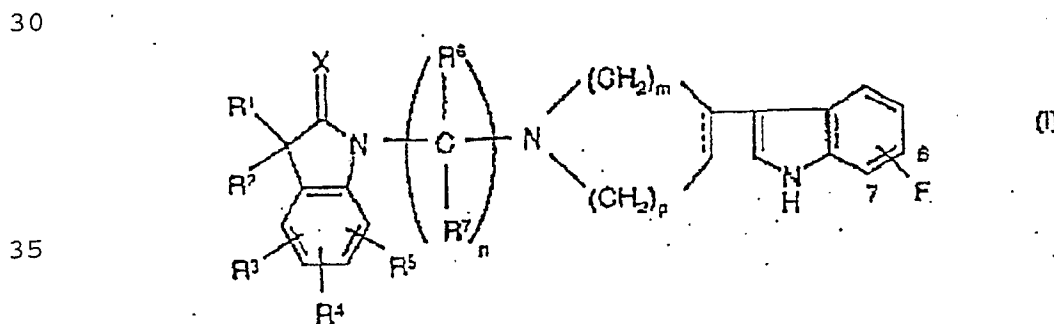
Pyrrolothiazine and pyrrolothiazepine compounds (see EP 0 970 088)





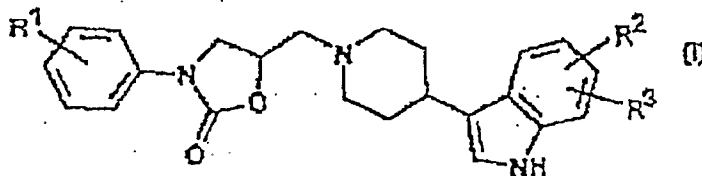
(a pyrrolesulfonamide derivative having formula (I) wherein the ring P represented by  $\alpha$  is a pyrrole ring having structure  $\beta$  or  $\gamma$  wherein R represents alkyl, cycloalkyl, cycloalkyl-alkyl or aralkyl; the dashed line indicates the presence or absence of a bond; and, when the bond is present, Z<sub>2</sub> is not present and Z<sub>1</sub> represents H but, when the bond is absent, Z<sub>1</sub> represents H and Z<sub>2</sub> represents OH or Z<sub>1</sub> and Z<sub>2</sub> are combined together to represent O or a group NOR<sub>1</sub>, in which R<sub>1</sub> represents H, or alkyl, aralkyl or aryl;  $\ell$  stands for 0 or 1; A represents alkylene, alkenylene or alkynylene; and Y represents a group 1 in which W represents CH, C= or N; m stands for 0 or 1 when W is CH or N, or m stands for 1 when W is C=; B represents a specific divalent group; E<sub>1</sub> and E<sub>2</sub> each independently represents H or lower alkyl; and D represents an aromatic hydrocarbon group or heterocyclic group),

indole derivatives (see WO 99/58525 and WO 00/49017) with the following structures (see also WO 99/47511).

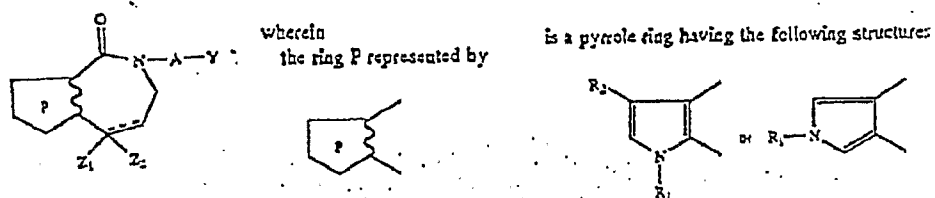


preferably 3-(piperidin-3-yl)-1 H indole compounds (see WO 98/38189).

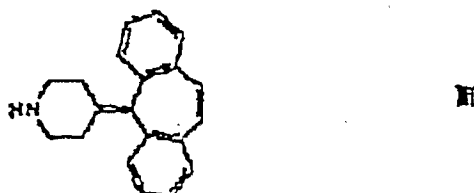
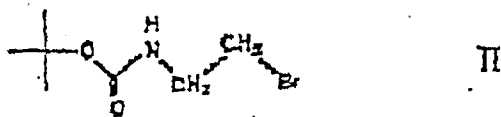
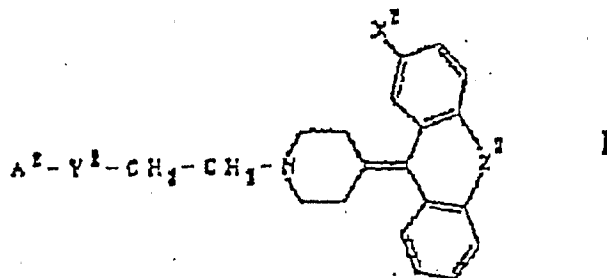
oxazolidine compounds (indole compounds) with the following structure



pyrroloazepine compounds with the following structures (see US 5,962,448).



Piperidine derivatives (JP 11246526)



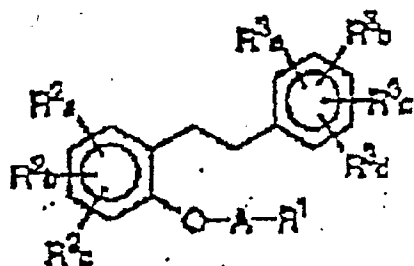
pyrrole sulphonamide-based compounds (see JP 11193290),

substituted 1,2,3,4-tetrahydronaphtalene derivatives (see EP 0 888 319), preferably

5 piperidinyl and piperazinyl substituted 1,2,3,4-tetrahydronaphtalene compounds,

benzothiazine derivatives (see US 5,874,429),

2-{2-[4-fluoro-2-(2-phenylethyl)phenoxy]ethyl}-4-hydroxy-1-methylpyrrolidine (see JP 11158067)



and biphenyl derivatives (see US 5,849,912),

and ALEPH-2, amperozide, amesergide, aryloxyalkylimidazoles, 1-aryl-4-propylpiperazines, BIMT 17, 1-3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-6-fluoroindolin-2(1H)-one, CGS 18102A, cinanserin, clonidine, cyproheptadine, deramciclane, desmethyl-WAY 100635, dotarizine, DV 7028, elymoclavine, fananserin, 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine, 8-[3-(4-fluorobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, FG5893 hydrochloride, FG5974, FG5983, hexahydrocarbazoles, (3H)WAY 100635, ICI 169,369, 8-[3-(4-iodobenzoyl)propyl]-1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, LEK-8804, loxapine, LSD, LU 111995, LY53857, (S,S)-LY-53,857, (R,S)-LY-53,857, (S,R)-LY-53,857, (R,R)-LY-53,857, LY-53,857 free base, LY 215840, MDL-11,939, MDL 28133A, MDL 100,151, MDL 100,907, mesulergine, Metergoline, Metergoline fenylmethyl ester, 1-3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl indolin-2(1H)-one, methysergide, Mianserin, NE-100, N-desmethyldiazepam, Nefazodone, N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, NRA0045, olanzapine, ondansetron, 1-(2-pyrimidinyl)piperazine



- derivatives, pirenpirone, pizotifen, pizotyline, promethazine, raclopride, roxindole, risperidone, ritan-serin, RP62203, sarpogrelate and its active metabolite (M-1), serotonin reuptake inhibitors like fluoxetine,
5. YM 992, medifoxamine, cericlamine, imipramine, iprindole, BIMT 17, citalopram, paroxetine, sertraline, sulpride (+)-, fluvoxamine, spiro indoles N-substituted with a 3-(dimethylamino)propyl chain, spiperone, SR 46349B, thioridazine, WAY 100635, WY-50,324, MDL 100,907,
- 10 LY-53,857 maleate, Pirenperone, Sulpiride (+-)+.

The most preferred 5-HT<sub>2</sub> antagonist is 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine.

The preferred combinations of 5-HT<sub>3</sub> and 5-HT<sub>2</sub> antagonists are the following:

- 15 - 3-(1-piperazinyl)-2-quinoxalinecarbonitrile and 4(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine
- 3-(1-piperazinyl)-2-quinoxalinecarbonitrile and AMI-193
- 3-(1-piperazinyl)-2-quinoxalinecarbonitrile and
- 20 MDL 119395
- Tropanyl 3,5-dimethylbenzoate and 4(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine
- Tropanyl 3,5-dimethylbenzoate and AMI-193
- Tropanyl 3,5-dimethylbenzoate and MDL 11939
- 25 - VB20B7 and 4(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine
- VB20B7 and AMI-193
- VB20B7 and MDL 11939
- MDL 72222 and Cinanserin
- 30 - 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole and AMI-193
- 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole and 4(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine

- 35 The present invention is also intended to comprise derivatives and analogs of the 5-HT<sub>4</sub> receptor antagonists, 5-HT<sub>3</sub> receptor antagonists and 5-HT<sub>2</sub> receptor

antagonists mentioned above having the same or essential same airway relaxation effect.

The present invention also relates to a method for treatment of disorders involving airway constriction, wherein said method comprises the administration to a human or animal patient of a therapeutically effective amount of a composition comprising a combination of a) at least one compound with antagonist activity to the 5-HT<sub>3</sub> receptor and b) at least one compound with antagonist activity to the 5-HT<sub>2</sub> receptor. Preferably, said method relates to the treatment of asthma, chronic bronchitis, emphysema and chronic obstructive pulmonary disease.

The typical daily dose of the medicament prepared according to the invention varies within a wide range and will depend on various factors such as the individual requirement of each patient and the route of administration.

In said combination of compounds with 5-HT<sub>3</sub> and 5-HT<sub>2</sub> antagonist activity, the relative amount of either compound may vary, but typically are about equal.

Said medicament may be prepared as a composition adapted either for administration via the respiratory tract or for oral, intravenous, intramuscular, subcutaneous, intrathecal, topical, or intraperitoneal administration, in association with one or more pharmaceutically acceptable carriers, diluents or adjuvants that are well known in the art.

Said medicament is preferably administered via the respiratory tract in the form of e.g. an aerosol or an air-suspended fine powder. However, in some cases useful alternative administration forms are tablets, capsules, powders, microparticles, granules, syrups, suspensions, solutions, transdermal patches or suppositories.

#### Detailed Description of the Invention

The subject-matter of the present invention was inter alia deduced from animal experiments, where a specific behaviour of the airway smooth muscle called

"spontaneous tone" was examined. The spontaneous tone, which involves a spontaneous continuous contraction in the airway smooth muscle, was studied due to a suspicion that a defective regulation of the spontaneous tone could  
5 be an important cause of the bronchoconstriction observed in asthmatic patients.

The examinations of the spontaneous tone were performed in accordance with the methods disclosed in the thesis "*Regulation of spontaneous tone in guinea pig*  
10 *trachea*" by S. Skogvall, Department of Physiological Sciences, Lund University, 1999, which is incorporated herein by reference. As evidenced by these examinations, the airways normally display a highly regular type of oscillating tone in physiological conditions, and this  
15 tone can be reversibly affected by administration of various substances.

In short, the animal experiments in said thesis showed that the spontaneous tone to a large degree is controlled by powerful regulating factors released from a  
20 specific type of airway epithelium cells, so-called neuroepithelial endocrine (NEE) cells.

Later experiments, not included in the thesis, have revealed that one of the released factors is serotonin (5-HT), which activates 5-HT<sub>2</sub>, 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors,  
25 among several others. Additional experiments showed that when a small dose (1  $\mu$ M) of 5-HT was added to guinea pig airway smooth muscle preparations displaying a strong, smooth spontaneous tone, a transient contraction was observed. A contractile effect of 5-HT on airways has  
30 previously been reported, see e.g. Skogvall, S., Korsgren, M., Grampp, W., J. Appl. Phys., 86:789-798, 1999. However, when a large dose (100  $\mu$ M) of 5-HT was used, the spontaneous tone was, after a transient contraction, significantly suppressed to a level of about  
35 half the force observed in control (drug-free) conditions. The spontaneous tone returned to approximately its normal (pre-treatment) level when 5-HT was removed. Thus,

it has now unexpectedly been shown that 5-HT causes a contraction of guinea pig airways at low concentrations and a relaxation at high concentrations, i.e. a dual effect. Furthermore, it was found that the 5-HT<sub>2a</sub> receptor antagonist ketanserin almost completely abolished the contraction but did not affect the relaxation, demonstrating that the contraction and relaxation was caused by activation of different receptors.

Similar experiments have also been performed on human airway preparations from patients undergoing lobectomy or pulmectomy due to lung cancer. In humans, 5-HT was even more potent in relaxing the airway smooth muscle than in guinea pig: even as low a concentration as 1  $\mu$ M 5-HT induced a significant relaxation in preparations displaying a spontaneous tone.

Human airways are generally considered to display only a weak contraction when exposed to 5-HT. Nevertheless, our examinations of spontaneous tone on human in vitro preparations have shown that 5-HT indeed causes a contraction also in this tissue. However, this contraction takes a longer time to develop than in guinea pig and the contractile effect is seen as a termination of the relaxation, rather than an increase of tone from the baseline (pre-treatment) level. The relaxation, which has a maximum after 10-15 min, disappears gradually during the following 30-45 min (see Fig 1). In contrast, in guinea pig trachea, the first 5-HT-induced effect is a contraction which reaches a maximum after approximately 10 min, and this is followed, within approximately 30 min, by a relaxation below the pre-treatment level. The transient nature of the 5-HT relaxation in human airways is most likely caused by a simultaneous activation of the fast relaxing 5-HT<sub>4</sub> receptor, and an activation of slower contracting 5-HT<sub>3</sub> and 5-HT<sub>2</sub> receptors. This is clear, because activation of the relaxing 5-HT<sub>4</sub> receptor by a substance that lacks 5-HT<sub>3</sub> and 5-HT<sub>2</sub> receptor activating properties (such as RS 67333), results in a re-

laxation that is persistent and not transient. Further, unspecific agonists, such as 5-HT, can cause a sustained relaxation if the constricting 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors are simultaneously blocked.

5 As mentioned above, our experiments have shown that there is a continuous release of 5-HT in human airways, most likely from the NEE cells, and that this endogenous 5-HT stimulates the contracting 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors. This is clear because a blockade of 5-HT<sub>2</sub> and 5-HT<sub>3</sub> recep-  
10 tors caused a distinct smooth muscle relaxation in examined preparations, implying that the 5-HT<sub>2</sub>- and 5-HT<sub>3</sub>-mediated contraction is an important factor in the generation of spontaneous tone in human airways.

In SU 1 701 320 it is suggested that 5-HT may be of  
15 use as an addition to standard beta2 receptor stimulation for the treatment of acute asthma attacks. No receptor mechanism for the effect of 5-HT is disclosed in that patent. SU 1 701 320 is not relevant for the present application since we do not propose the use of 5-HT receptor  
20 agonists (such as 5-HT), but rather 5-HT receptor antagonists.

The action of this combination at two different receptors causes a greater airway relaxation than an action at only one receptor. Further, we have found that the  
25 most important contractile receptor in some individuals is 5-HT<sub>2</sub> and in others 5-HT<sub>3</sub>, which necessitates a combination of blocking substances.

In summary, it has now been discovered that inhibition of the 5-HT<sub>3</sub> receptor and/or the 5-HT<sub>2</sub> receptor results in airway relaxation. It was deduced from these  
30 experiments that compounds with antagonist activity to the 5-HT<sub>2</sub> receptor and compounds with antagonist activity to the 5-HT<sub>3</sub> receptor therefore are useful as agents for treatment of disorders involving airway constriction, as  
35 defined above.

Thus, the present invention relates to a composition comprising a combination of compounds comprising a) at

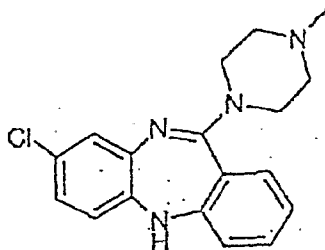
least one compound with antagonist activity to the 5-HT<sub>3</sub> receptor and b) at least one compound with antagonist activity to the 5-HT<sub>2</sub> receptor as a medicament. The present invention also relates to the use of said combination for the manufacture of a medicament intended for treatment of disorders involving airway constriction, wherein the administration of said combination can be simultaneous or sequential.

## CLAIMS

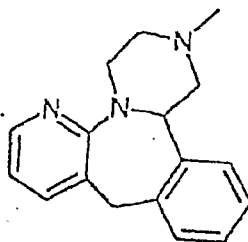
1. A composition comprising a combination of compounds comprising a) at least one compound with antagonist activity to the 5-HT<sub>3</sub> receptor, and b) at least one compound with antagonist activity to the 5-HT<sub>2</sub> receptor.

2. A composition according to claim 1, wherein said composition has the capacity of reducing pathological airway constriction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said combination is chosen from the following groups of 5-HT<sub>3</sub> antagonists and 5-HT<sub>2</sub> antagonists, or derivatives or pharmaceutically acceptable salts thereof.

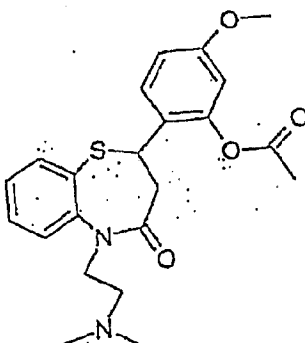
a) 5-HT<sub>3</sub> receptor antagonists



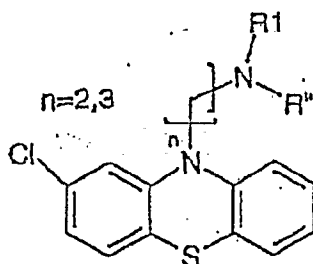
benzazepines, preferably mirtazapine



benzthiazepines, preferably diltiazem

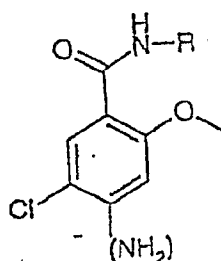


and fentiazines



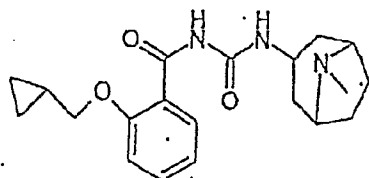
preferably perphenazine, chlorpromazine, stemetil;

10 compounds also having 5-HT<sub>4</sub> receptor agonist activity, preferably benzamides



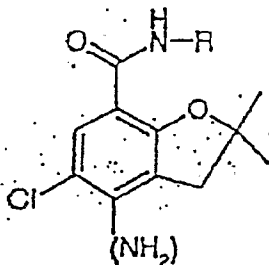
(cisapride, zacopride,  
mosapride, metoclopra-  
mide, pancopride,  
BRL 24924, BMY 33462)

and



WAY 100289

2,3-dihydro-benzofuran-7-carboxamides



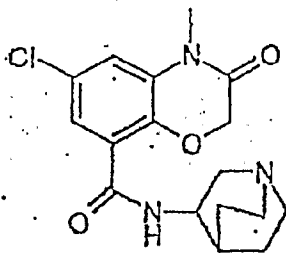
30 (preferably zatosetron=LY 277359, ADR 851);



104

1,4-benzoxazin-8-carboxamides

5

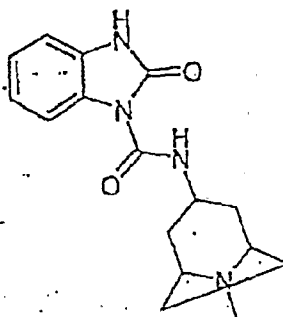


preferably azasetron (=Y25130)

10

benzimidazolones

15

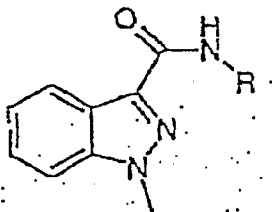


preferably itasetron (=DAU 6215);

20

indazol-3-carboxamides

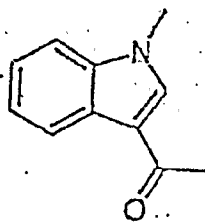
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preferably N 3389, LY 278584, DAT 582;

wherein the latter group reminds most of the  
specific 5-HT<sub>3</sub> antagonists, which contains the group

30

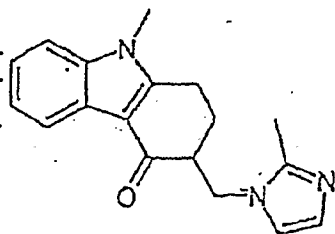


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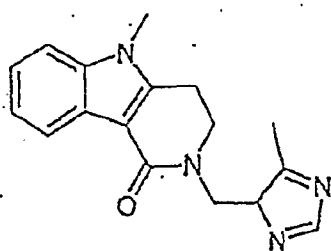
in different forms, such as

5

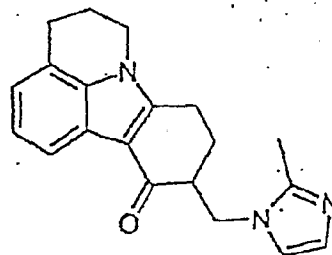


ondansetron

10



alosetron

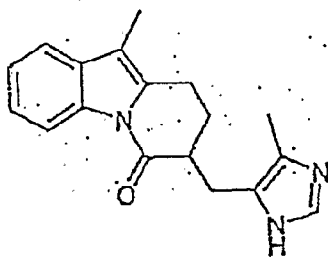


cilansetron

15

substances the structure of which has been inverted and  
the carbonyl group has been placed on the indoline  
nitrogen

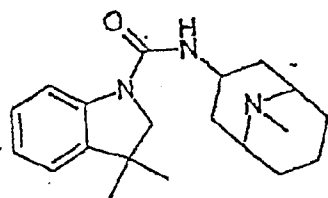
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FK 1052

also being an antagonist against both 5-HT<sub>3</sub> and 5-HT<sub>4</sub>  
receptors,

35

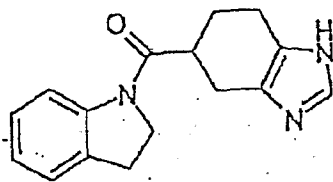


BRL 46470 A

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bisindoles

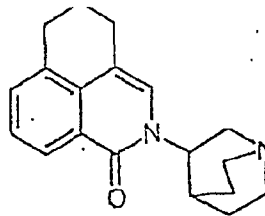
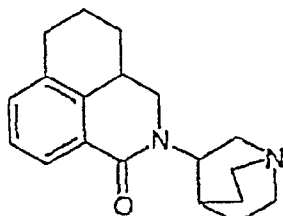
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YM 114

isoquinoline-1-ones

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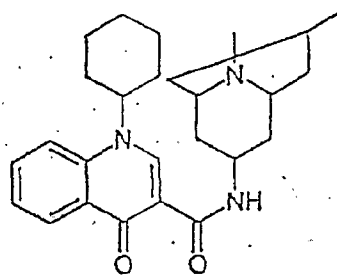
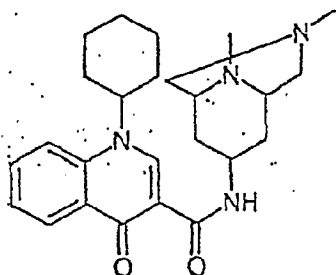
15

palonosetron (=RS 25259-197)

RS 42358-197

and the quinoline-3-carboxamides

20



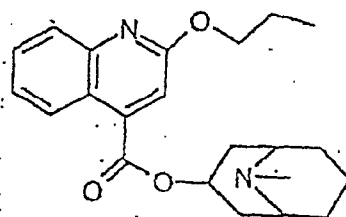
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WAY-SEC 579

Mirisetron (=WAY 100579),

quinoline-4-carboxylates

30

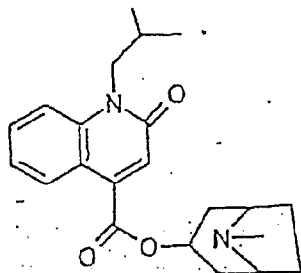


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preferably KF 17643

107

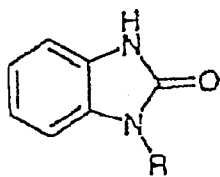
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preferably KF 18259;

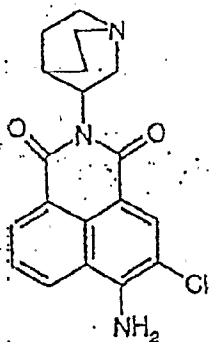
benzimidazolones

10



15 preferably droperidol (neurolidol), itasetron (DAU6215),  
and the naphthimides

20

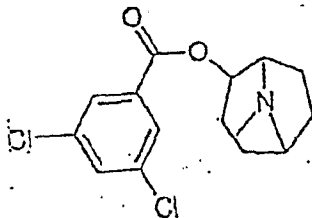


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preferably RS 56532;

MDL 72222, which also is a specific 5-HT<sub>3</sub>  
antagonist;

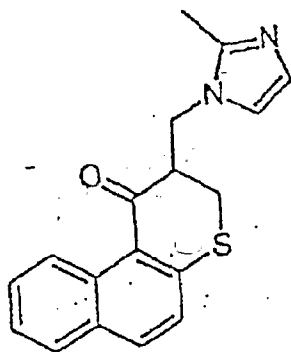
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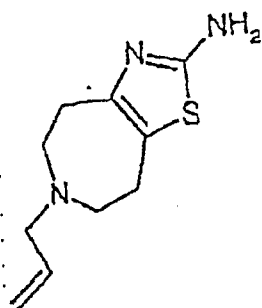
; and

5



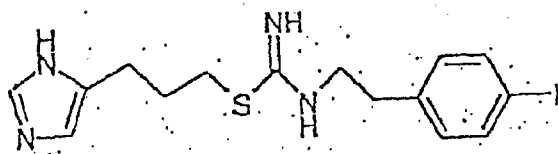
GK 128

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Talipexole

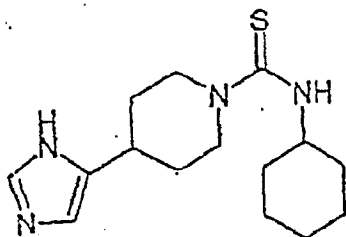
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iodophenpropit

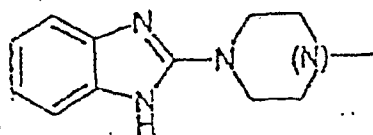
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thioperamide, and

30

2-piperidin- and 2-piperazin-  
benzimidazoles; and also

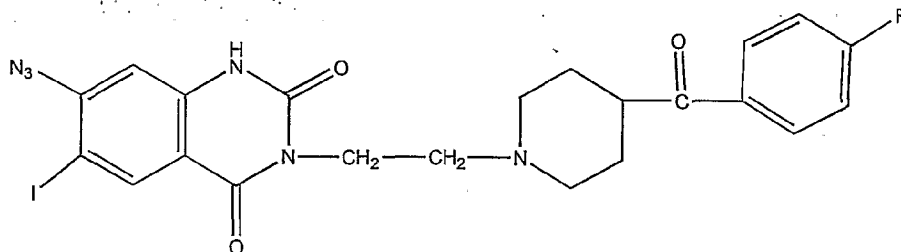
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(R)-zacopride, 2-methyl-5HT, 3-(1-piperazinyl)-2-quinoxalinecarbonitrile, 3-(4-allylpiperazin-1-yl)-2-quinoxalinecarbonitrile, 4-Ph-N-Me-quipazine, 5-((dime-

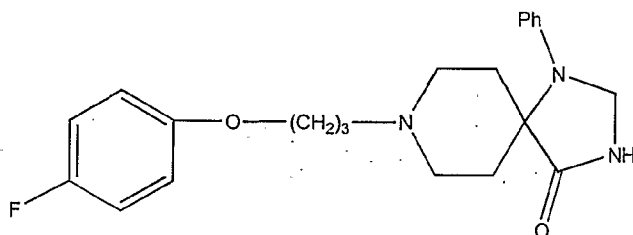
thylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, 5,7-DHT, 5-[(dimethylamino)methyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole, ADR-882, Amitriptyline, AS-5370, Batanopride, BIMU 1, BRL 24682, 5 BRL 43694, BRL 46470 (=Ricasetron), BRL 47204, Bufotenine, CF 109203 (=BIM), Cizapride, Clozapine, CP-93318, Cyameazine, Cyproheptadine, Dolasetron mesilat (=MDL 73147 EF), Fluphenazone, Galdanasetron, GR 38032 F, GR 67330, Granisetron (=Kytril=BRL 43694), GR-H, GYKL- 10 48903, ICS 205-930, Imipramine, Indalpine, KAE-393/-YM-114, KB-6922, KB-6933, KB-R 6933, KF-20170, Leri-setron, Lurosetron, LY 258-458, LY 278-989, LY-211-000, McNeil-A-343, MCPP, MDL 72699, Mepyramine, Metergoline, Methysergide, Mianserin, MK 212, N-3256, NAN-190, N- 15 metylquipazin, 3-(1-piperaziny)-2-quinoxalinecarbo-nitrile, ONO-3051, Pancopride, Phenylbiguanide, Pitozifen, Prochlorperazine, QICS 205-930, R(+)zacopride, Renzapride, RG 12915, Ritanserin, RP 62203, RS-056812-198, RS-25259, RU 24969, S(-)Zacopride, S-apomorfin, 20 SC-52491, SC-53116, SDZ 206-792, SDZ 206-830, SDZ 210-204, SDZ 210-205, SDZ 214-322, SDZ 322, SN-307, TFMPP, TMB 8, Trifluoperzine, tropanyl-3,5-dimethylbenzoate, 3-tropanyl-indole-3-carboxylate methiodide, VA 21 B 7, Y 2513, zelmac, SEC 579, BRL 46470 A, Pizo- 25 tifen, Dolasetron (=MDL 74156), Galanolactone, GR 65 630, Ifenprodil, L-683877, Litoxetine, Quipazine, QX 222, Ramosetron (=YM 060), RS 56812, SDZ 216-525, Trimebutine, GR 65630, Tropisetron, Bemasetron, L-683,877, LY-278, 584 maleate and pharmaceutically acceptable salts thereof 30 with the same or essentially the same relaxation enhanc-ing effect, and

110

b) 5-HT<sub>2</sub> receptor antagonists: Ketanserin, i.e. 7-azido-3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-6-iodo-2,4(1H, 3H)-quinazolinedione, having the structural formula:

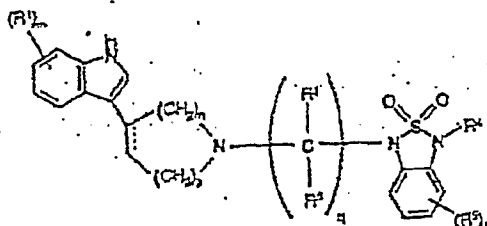


AMI-193, i.e. 8-[3-(4-fluorophenoxy)propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, having the structural formula:



10

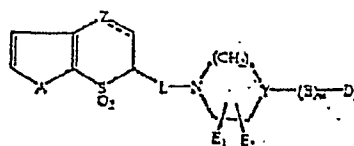
1-((indolyl azacycloalkyl)alkyl)-2,1,3-benzothiadiazole 2,2-dioxides with the following structure:



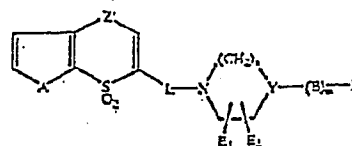
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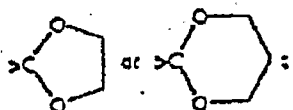
thiopyran derivatives represented by the following formula (I) or (I'), or the salt thereof:



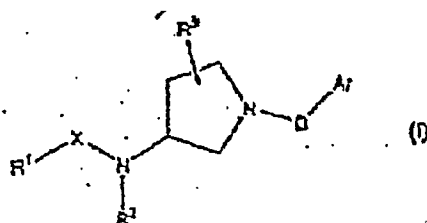
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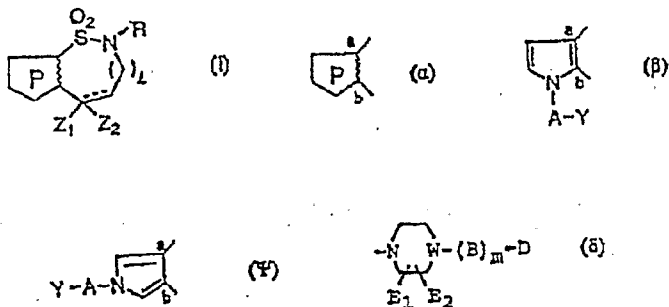
wherein A is S or  $-\text{CH}=\text{CH}-$ ; the dotted line indicates that the bond may be either present or absent; Z and Z' are typically



L is an ethylene or trimethylene group; Y is CH or N; n is 2; B is a carbonyl group; m is 0 or 1; D is a phenyl group; and E<sub>1</sub> and E<sub>2</sub> are hydrogen atoms, pyrrolidine compounds with the following structure:



pyrrolothiazine and pyrrolothiazepine compounds



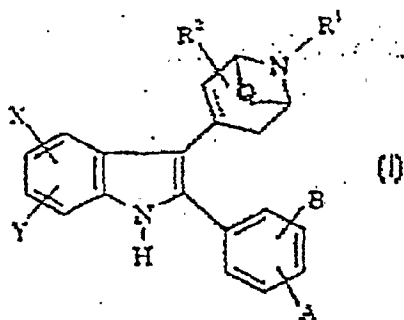
(a pyrrolesulfonamide compound having formula (I) wherein the ring P represented by  $\alpha$  is a pyrrole ring having structure  $\beta$  or  $\psi$  wherein A represents alkylene, alkenylene or alkynylene; and Y represents a group  $\delta$  in which W represents CH, C= or N; m stands for 0 or 1 when



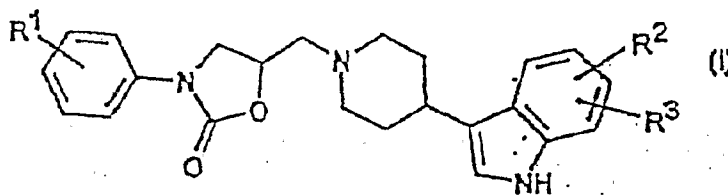
112

W is CH or N, or m stands for 1 when W is C=; B represents a specific divalent group; E<sub>1</sub> and E<sub>2</sub> each independently represents H or lower alkyl; and D represents an aromatic hydrocarbon group or heterocyclic group; *l* stands for 0 or 1; the dashed line indicates the presence or absence of a bond; and, when the bond is present, Z<sub>2</sub> is not present and Z<sub>1</sub> represents H but, when the bond is absent, Z<sub>1</sub> represents H and Z<sub>2</sub> represents OH or Z<sub>1</sub> and Z<sub>2</sub> are combined together to represent O or a group NOR<sub>5</sub>, in which R<sub>5</sub> represents H, or alkyl, aralkyl or aryl; and R represents H, alkyl, cycloalkyl, cycloalkyl-alkyl or aralkyl;

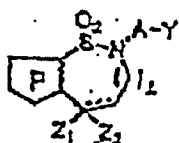
azabicyclo-substituted phenylindole derivatives with the following formula.



oxazolidines



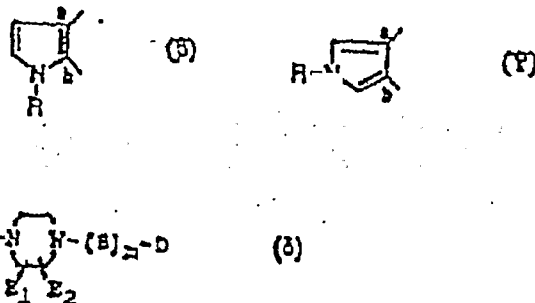
pyrrolothiazine and pyrrolothiazepine compounds



(III)



(IV)

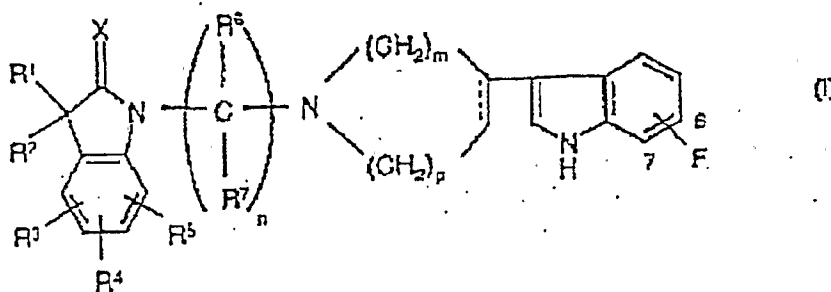


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(a pyrrolesulfonamide derivative having formula (I) wherein the ring P represented by  $\alpha$  is a pyrrole ring having structure  $\beta$  or  $\gamma$  wherein R represents alkyl, cycloalkyl, cycloalkyl-alkyl or aralkyl; the dashed line indicates the presence or absence of a bond; and, when the bond is present,  $Z_2$  is not present and  $Z_1$  represents H but, when the bond is absent,  $Z_1$  represents H and  $Z_2$  represents OH or  $Z_1$  and  $Z_2$  are combined together to represent O or a group  $NOR_1$ , in which  $R_1$  represents H, or alkyl, aralkyl or aryl;  $\ell$  stands for 0 or 1; A represents alkylene, alkenylene or alkynylene; and Y represents a group 1 in which W represents CH, C= or N; m stands for 0 or 1 when W is CH or N, or m stands for 1 when W is C=; B represents a specific divalent group;  $E_1$  and  $E_2$  each independently represents H or lower alkyl; and D represents an aromatic hydrocarbon group or heterocyclic group),

indole derivatives with the following structures.

30

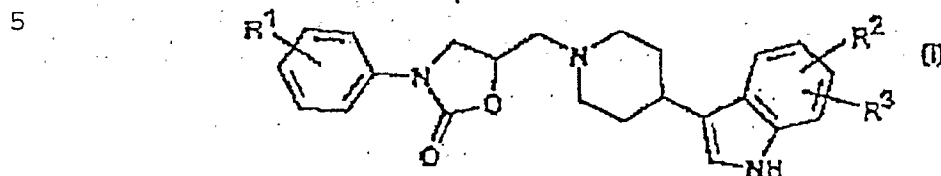


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preferably 3-(piperidin-3-yl)-1 H indole compounds,

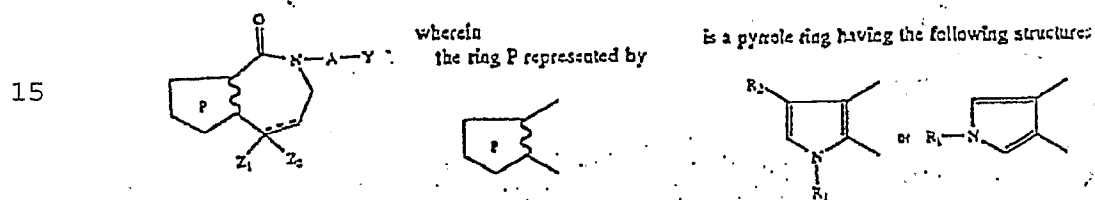
114

oxazolidine compounds (indole compounds) with the following structure



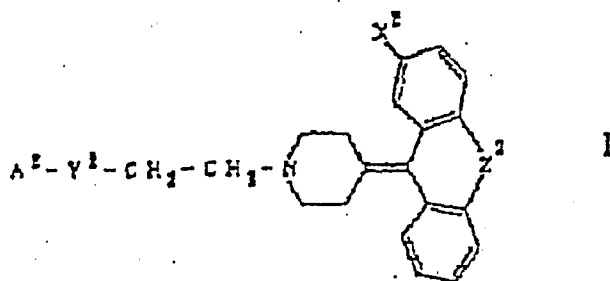
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pyrroloazepine compounds with the following structures:

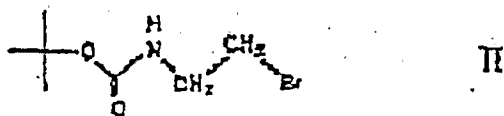


piperidine derivatives

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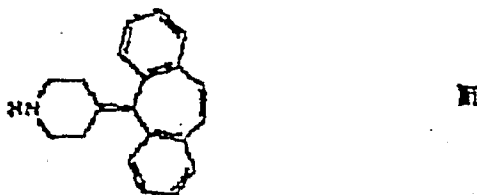


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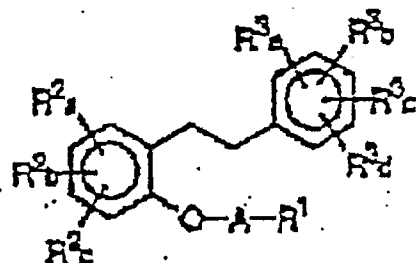
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pyrrole sulphonamide-based compounds,  
substituted 1,2,3,4-tetrahydronaphthalene  
derivatives,

piperidiny and piperaziny substituted 1,2,3,4-  
5 tetrahydronaphthalene compounds,  
benzothiazine derivatives,  
2-{2-[4-fluoro-2-(2-phenylethyl)phenoxy]ethyl}-4-  
hydroxy-1-methylpyrrolidine

10



15

and biphenyl derivatives;

LY-53,857 maleate, Pirenperone, Sulpiride (+-)+, and  
ALEPH-2, amperozide, amesergide, aryloxyalkylimidazolin-  
es, 1-aryl-4-propylpiperazines, BIMT 17, 1-3-[4-(3-  
20 chlorophenyl)-1-piperazinyl]propyl-6-fluoroindolin-  
2(1 H)-one, CGS 18102A, cinanserin, clonidine, cyprohep-  
tadine, deramciclone, desmethyl-WAY 100635, dotarizine,  
DV 7028, elymoclavine, fananserin, 4-(4-fluorobenzoyl)-1-  
(4-phenylbutyl)-piperidine, 8-[3-(4-fluorobenzoyl)propyl]-  
25 1-methyl-1,3,8-triazaspiro[4,5]decan-4-one, FG5893 hydro-  
chloride, FG5974, FG5983, hexahydrocarbazoles, (3H)WAY  
100635, ICI169,369, 8-[3-(4-iodobenzoyl)propyl]-1-methyl-  
1,3,8-triazaspiro[4,5]decan-4-one, LEK-8804, loxapine,  
LSD, LU 111995, LY53857, (S,S)-LY-53,857, (R,S)-LY-  
30 53,857, (S,R)-LY-53,857, (R,R)-LY-53,857, LY-53,857 free  
base, LY 215840, MDL-11,939, MDL 28133A, MDL 100,151,  
MDL 100,907, mesulergine, Metergoline, Metergoline fenyl-  
methyl ester, 1-3-[4-(2-methoxyphenyl)-1-piperazinyl]-  
propyl indolin-2(1H)-one, methysergide, Mianserin,  
35 NE-100, N-desmethyldiazepam, Nefazodone, N-ethoxy-  
carbonyl-2-ethoxy-1,2-dihydroquinoline, NRA0045, olanza-  
pine, ondansetron, 1-(2-pyrimidinyl)piperazine deriva-

tives, pirenpirone, pizotifen, pizotyline, promethazine, raclopride, roxindole, risperidone, ritanserin, RP62203, sarpogrelate and its active metabolite (M-1), serotonin reuptake inhibitors like fluoxetine, YM 992, medifox-  
5 amine, cericlamine, imipramine, iprindole, BIMT 17, citalopram, paroxetine, sertraline, sulpride ( $\pm$ )-, fluvoxamine, spiro indoles N-substituted with a 3-(dimethyl-amino)propyl chain, spiperone, SR 46349B, thioridazine, WAY 100635, WY-50,324, MDL 100,907.

10 3. Composition according to claim 2, wherein it comprises a combination of compounds selected from one of the following combination of 5-HT<sub>3</sub> receptor antagonists, and 5-HT<sub>2</sub> receptor antagonists;

- 3-(1-piperazinyl)-2-quinoxalinecarbonitrile and 4(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine  
15

- 3-(1-piperazinyl)-2-quinoxalinecarbonitrile and AMI-193

- 3-(1-piperazinyl)-2-quinoxalinecarbonitrile and MDL 119395

20 - Tropanyl 3,5-dimethylbenzoate and 4(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine

- Tropanyl 3,5-dimethylbenzoate and AMI-193

- Tropanyl 3,5-dimethylbenzoate and MDL 11939

- VB20B7 and 4(4-fluorobenzoyl)-1-(4-phenylbutyl)-  
25 piperidine

- VB20B7 and AMI-193

- VB20B7 and MDL 11939

- MDL 72222 and Cinanserin

- 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole and AMI-193  
30

- 5-((dimethylamino)methyl)-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole and 4(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine

35 4. Composition according to claim 2 for use as a medicament.

5. Composition according to claim 3 for use as a medicament.

6. Use of a composition comprising a combination of compounds comprising a) at least one compound with antagonist activity to the 5-HT<sub>3</sub> receptor, and b) at least one compound with antagonist activity to the 5-HT<sub>2</sub> receptor for the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving airway constriction, chosen from the group consisting of asthma, emphysema, chronic bronchitis and chronic obstructive pulmonary disease.
- 10 7. Use according to claim 6 of a composition as defined in claim 2.
8. Use according to claim 7 of a composition as defined in claim 3.
- 15 9. A method for the treatment of disorders involving airway constriction chosen from the group consisting of asthma, emphysema, chronic bronchitis and chronic obstructive pulmonary disease, wherein said method comprises administration of a therapeutically effective amount of a composition according to any one of claims
- 20 1-3.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/02373

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/395, A61K 31/4045, A61P 11/06, A61P 11/08  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0064441 A2 (RESPIRATORIUS AB), 2 November 2000 (02.11.00), claims 1-17 --	3,5,8
X	TINS, September 1986, Brian P. Richardson et al: The pharmacology and function of 5-HT3 receptors", sid 424 - sid 428, tabell II --	3,5,8
X	Drug Development Research, Volume 13, 1998, Mark W. Dudley et al, "Pharmacological Effects of MDL 11,939: A Selective, Centrally Acting Antagonist of 5-HT2 Receptors", page 29 - page 43, table 1B --	3,5,8

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

7 February 2002

Date of mailing of the international search report

15-02-2002

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/02373

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Med. Chem., Volume 34, 1991, C. J. Swain et al, "Novel 5-HT <sub>3</sub> Antagonists. Indole Oxadiazoles", page 140 - page 151, page 140  --	3,5,8
X	WO 9943319 A1 (THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS), 2 Sept 1999 (02.09.99), claim 3  --	3,5,8
X	Eur Respir J, Volume 14, 1999, L.J. Dupont et al, "The effects of 5-HT on cholinergic contraction in human airways in vitro", page 642 - page 649, figure 4  --	3,5,8
X	Chem. Pharm. Bull., Volume 48, No. 5, 2000, Akira Mizuno et al, "Synthesis and Serotonin 2 (5-HT <sub>2</sub> ) Receptor Antagonist Activity of 5-Aminoalkyl-substituted Pyrrolo(3,2-c)azepines and Related Compounds", page 623 - page 635, compound 18a  --	3,5,8
A	TiPS, Volume 21, January 2000, Mario Cazzola et al, "5-HT modifiers as a potential treatment of asthma", page 13 - pge 16, 5-HT receptors and airways  --	1-9
P,A	US 6169105 A (DAVID TAIWAY WONG ET AL), 2 January 2001 (02.01.01), claims 1-5  --	1-9
A	WO 0110423 A2 (NOVARTIS-ERFINDUNGEN), 15 February 2001 (15.02.01), claims 1-8  --	3,5,8
A	Clinics in Chest Medicine, Volume 10, No. 1, March 1989, C. Michael Hart et al: "Lung Serotonin Metabolism", page 59 - page 70  -- -----	1-9



# INTERNATIONAL SEARCH REPORT

International application No.  
**PCT/SE01/02373**

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **1, 2, 4, 6, 7**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see next sheet**
2. ☒ Claims Nos.: **9**  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
**see next sheet**
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

**Box I.1**

The claims contain a plurality of different compounds and parameters which render it difficult, if not impossible to determine the matter for which protection is sought. The present application therefore fails to comply with the clarity and conciseness requirements of Article 6 PCT such an extent that a meaningful search of the whole scope of the claims is impossible.

Expressions such as " compound with agonist activity to a 5-HT4 receptor" or "at least one compound with antagonist activity to a 5-HT3 receptor" or " at least one compound with antagonist activity to a 5-HT2 receptor" are unclear and defined in terms of the result to be achieved. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art.

Consequently, the search has mainly been carried out for those parts which appear to be clear, supported and disclosed, namely claim 3 and those parts of claims 5 and 8 relating to claim 3.

**Box I.2**

Claim 9 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

27/12/02

International application No.

PCT/SE 01/02373

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	0064441	A2	02/11/00	AU	5259100 A	10/11/00
				AU	5895099 A	27/03/00
				EP	1109443 A	27/06/01
				SE	9901531 D	00/00/00
				AU	1429400 A	22/05/00
				EP	1123219 A	16/08/01
				SE	9901906 D	00/00/00
				US	2001030451 A	18/10/01
				AU	2016000 A	03/07/00
				AU	5861900 A	02/01/01
				EP	1152834 A	14/11/01
				SE	9902251 D	00/00/00
				WO	0076500 A	21/12/00
				AU	2016100 A	19/06/00
				EP	1135683 A	26/09/01
				SE	9902252 D	00/00/00
WO	9943319	A1	02/09/99	EP	1066036 A	10/01/01
				EP	1077678 A	28/02/01
				US	5942243 A	24/08/99
				WO	9958110 A	18/11/99
US	6169105	A	02/01/01	CA	2163840 A	29/05/96
				EP	0714663 A	05/06/96
				JP	8208471 A	13/08/96
WO	0110423	A2	15/02/01	AU	6991300 A	05/03/01
				GB	9918425 D	00/00/00